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- (71) Applicant (*for all designated States except US*): CORIXA CORPORATION [US/US]; Suite 200, 1124 Columbia Street, Seattle, WA 98104 (US).
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- (72) Inventors; and
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(54) Title: OVARIAN TUMOR SEQUENCES AND METHODS OF USE THEREFOR

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Polypeptides and polynucleotides as provided herein may further be used for the detection and monitoring of ovarian cancer.

INTERNATIONAL SEARCH REPORT

International Application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/00 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 37418 A (CORIXA CORP) 27 August 1998 (1998-08-27) SEQ ID 74, pos. 349-438 (100% identity) page 67	1-65
X	--- DATABASE EMBL [Online] accession no. AF060226, 6 May 1998 (1998-05-06) PIRTSKHALAISHVILI, G. ET AL.: "Transduction of dendritic cells ..." XP002153258 96.6% identity in 89 bp overlap abstract --- -/--	1-65

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

Date of the actual completion of the international search

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21.03.01

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL [Online] accession no. X02662, 7 May 1999 (1999-05-07) ENSSER A. AND FLECKENSTEIN B.: "Semaphorin L." XP002153259 96.6% identity in 89 bp overlap abstract</p> <p>---</p>	1-65
X	<p>DATABASE EMBL [Online] accession no. AA536804, 31 July 1997 (1997-07-31) MARRA, M. ET AL.: "The WashU-HHMI mouse EST project" XP002153260 70.9% identity in 278 bp overlap abstract</p> <p>---</p>	1-65
A	<p>MEDEN H ET AL: "Overexpression of the oncogene c-erbB-2 (HER2/neu) in ovarian cancer: a new prognostic factor." EUROPEAN JOURNAL OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE BIOLOGY, (1997 FEB) 71 (2) 173-9. REF: 36, XP000943740 the whole document</p> <p>---</p>	
T	<p>DATABASE EMBL [Online] accession no. AC016957, 14 December 1999 (1999-12-14) MUZNEY, D. M. ET AL.: "Homo sapiens clone RP11-50I19" XP002153261 100% identity in 278 bp overlap abstract</p> <p>---</p>	1-65
T	<p>DATABASE EMBL [Online] accession no. AX001326, 10 March 2000 (2000-03-10) FLECKENSTEIN B. P. AND ENSSER, A. D.: "Human and murine semaphorin L" XP002153262 96.6% identity in 89 bp overlap abstract</p> <p>-----</p>	1-65

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/24827

Box I Observations where certain claims were found uns archabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **36-45**
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-65 (part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-65 (part)

potential invention 1: nucleotides encoding "ovarian carcinoma proteins" encoded by the SEQ ID 1, polypeptides and polypeptide fragments encoded thereby and related matter (claims 1-65, part.)

2. Claims: 1-65 (part)

potential inventions 2-97: nucleotides encoding "ovarian carcinoma proteins" encoded by the remaining SEQ IDs cited in claims 1, polypeptides and polypeptide fragments encoded thereby and related matter

3. Claims: 18-65 (part)

potential inventions 98-198: uses of known "ovarian carcinoma proteins" encoded by the remaining SEQ IDs 3, 4, 6-9 195-199 (except 186), and related matter

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9837418 A	27-08-1998	AU 6536898 A	09-09-1998
		BR 9807734 A	31-10-2000
		EP 0972201 A	19-01-2000
		ZA 9801536 A	08-01-1999

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WO 01/18046 A2

(54) Title: **OVARIAN TUMOR SEQUENCES AND METHODS OF USE THEREFOR**

(57) **Abstract:** Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Polypeptides and polynucleotides as provided herein may further be used for the detection and monitoring of ovarian cancer.

OVARIAN TUMOR SEQUENCES AND METHODS OF USE THEREFOR

TECHNICAL FIELD

The present invention relates generally to ovarian cancer therapy. The invention is more specifically related to polypeptides comprising at least a portion of an ovarian carcinoma protein, and to polynucleotides encoding such polypeptides, as well as antibodies and immune system cells that specifically recognize such polypeptides. Such polypeptides, polynucleotides, antibodies and cells may be used in vaccines and pharmaceutical compositions for treatment of ovarian cancer.

10 BACKGROUND OF THE INVENTION

Ovarian cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and therapy of this cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Management of the disease currently relies on a combination of early diagnosis and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. However, the use of established markers often leads to a result that is difficult to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer treatment and survival. Such therapies may involve the generation or enhancement of an immune response to an ovarian carcinoma antigen. However, to date, relatively few ovarian carcinoma antigens are known and the generation of an immune response against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for identifying ovarian tumor antigens and for using such antigens in the therapy of ovarian cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, this invention provides compositions and methods for the therapy of cancer, such as ovarian cancer. In one aspect, the present invention provides polypeptides comprising an immunogenic portion of an ovarian carcinoma protein, or a
5 variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished. Within certain embodiments, the ovarian carcinoma protein comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19,
10 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185 and 193-199, and complements of such polynucleotides.

The present invention further provides polynucleotides that encode a
15 polypeptide as described above or a portion thereof, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions and vaccines. Pharmaceutical compositions may comprise a physiologically acceptable carrier or excipient in combination with one or more of: (i) a
20 polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a
25 sequence recited in any one of SEQ ID NOs:1-185 and 187-199; (ii) a polynucleotide encoding such a polypeptide; (iii) an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide. Vaccines may comprise a non-specific immune response enhancer in combination with one or more of: (i) a
30 polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or

insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NOs:1-185 and 187-196, (ii) a polynucleotide
5 encoding such a polypeptide; (iii) an anti-idiotypic antibody that is specifically bound by an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide. An exemplary polypeptide comprises an amino acid sequence recited in SEQ ID NO:186.

10 The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

 Within related aspects, pharmaceutical compositions comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a
15 physiologically acceptable carrier are provided.

 Vaccines are further provided, within other aspects, comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a non-specific immune response enhancer.

 Within further aspects, the present invention provides methods for
20 inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

 The present invention further provides, within other aspects, methods for stimulating and/or expanding T cells, comprising contacting T cells with (a) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a
25 variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NOs:1-185 and 187-199; (b) a polynucleotide
30 encoding such a polypeptide and/or (c) an antigen presenting cell that expresses such a polypeptide under conditions and for a time sufficient to permit the stimulation and/or

expansion of T cells. Such polypeptide, polynucleotide and/or antigen presenting cell(s) may be present within a pharmaceutical composition or vaccine, for use in stimulating and/or expanding T cells in a mammal.

Within other aspects, the present invention provides methods for
5 inhibiting the development of ovarian cancer in a patient, comprising administering to a patient T cells prepared as described above.

Within further aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a
10 polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a
15 sequence recited in any one of SEQ ID NOs:1-185 and 187-199; (ii) a polynucleotide encoding such a polypeptide; or (iii) an antigen-presenting cell that expresses such a polypeptide; such that T cells proliferate; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of ovarian cancer in the patient. The proliferated cells may be cloned prior to
20 administration to the patient.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

25 **DETAILED DESCRIPTION OF THE INVENTION**

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly ovarian cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding
30 such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs)

and immune system cells (e.g., T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of
5 the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, e.g., Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid
10 Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

15 As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

POLYPEPTIDE COMPOSITIONS

20 As used herein, the term "polypeptide" is used in its conventional meaning, i.e. as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-
25 expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, i.e. antigenic
30 determinants substantially responsible for the immunogenic properties of a polypeptide

and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth herein, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a
5 polynucleotide sequence set forth herein.

The polypeptides of the present invention are sometimes herein referred to as ovarian tumor proteins or ovarian tumor polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in ovarian tumor samples. Thus, a "ovarian tumor polypeptide" or "ovarian tumor
10 protein," refers generally to a polypeptide sequence of the present invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of ovarian tumor samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of ovarian tumor samples tested, at a level that is at least two fold, and preferably
15 at least five fold, greater than the level of expression in normal tissues, as determined using a representative assay provided herein. A ovarian tumor polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

20 In certain preferred embodiments, the polypeptides of the invention are immunogenic, i.e., they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with ovarian cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as
25 those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one illustrative example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

30 As would be recognized by the skilled artisan, immunogenic portions of

the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide.

5 Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they

10 specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that

15 is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that

20 have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain

25 have been deleted. Other illustrative immunogenic portions will contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells

30 and/or antibodies generated against a polypeptide of the invention, particularly a

polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies
5 that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

10 The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide compositions encoded by a polynucleotide sequence set forth herein.

In another aspect, the present invention provides variants of the
15 polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described below), along its length, to a polypeptide sequences set forth herein.

20 In one preferred embodiment, the polypeptide fragments and variants provide by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set for the herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least
25 about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more

substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein and/or using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the

disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU			
Cysteine	Cys	C	UGC	UGU					
Aspartic acid	Asp	D	GAC	GAU					
Glutamic acid	Glu	E	GAA	GAG					
Phenylalanine	Phe	F	UUC	UUU					
Glycine	Gly	G	GGA	GGC	GGG	GGU			
Histidine	His	H	CAC	CAU					
Isoleucine	Ile	I	AUA	AUC	AUU				
Lysine	Lys	K	AAA	AAG					
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU	
Methionine	Met	M	AUG						
Asparagine	Asn	N	AAC	AAU					
Proline	Pro	P	CCA	CCC	CCG	CCU			
Glutamine	Gln	Q	CAA	CAG					
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU	
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU	
Threonine	Thr	T	ACA	ACC	ACG	ACU			
Valine	Val	V	GUA	GUC	GUG	GUU			
Tryptophan	Trp	W	UGG						
Tyrosine	Tyr	Y	UAC	UAU					

5

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative

10 hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other

molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine
5 (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a
10 protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on
15 the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity
20 values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 \pm 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino
25 acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-

translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

5 When comparing polypeptide sequences, two sequences are said to be “identical” if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A “comparison
10 window” as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

 Optimal alignment of sequences for comparison may be conducted using
15 the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical
20 Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-
25 425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

 Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL.*
30 *Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J.*

Mol. Biol. 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI),
5 or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST
10 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted
15 when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

20 In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference
25 sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by
30 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes
5 (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide
10 to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels,
15 relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames
20 of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is
25 incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with
30 the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be

used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see, for example, Stoute et al. New Engl. J. Med.*, 336:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a *Mycobacterium* sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; *see also, Skeiky et al., Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding

sequence express at high levels and remain as a soluble polypeptides throughout the purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid
5 residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that
10 encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70%
15 identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises
20 approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to
25 increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

30 In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is

derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible
5 for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see *Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of
10 LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting
15 signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4⁺ T-cells specific for the polypeptide.

20 Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are
25 synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and
30 may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, e.g., are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

POLYNUCLEOTIDE COMPOSITIONS

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules

and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably and
5 immunogenic variant or derivative, of such a sequence.

Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-185 and 187-196, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-185 and 187-196, and
10 degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-185 and 187-196. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in
15 SEQ ID NOs: 1-185 and 187-196, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide sequence of this invention using the methods described herein, (e.g., BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be
20 appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the
25 polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompass homologous genes of xenogenic origin.

In additional embodiments, the present invention provides
30 polynucleotide fragments comprising various lengths of contiguous stretches of

sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all
5 intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

10 In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent
15 conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be
20 readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, e.g., to 60-65°C or 65-70°C.

25 In certain preferred embodiments, the polynucleotides described above, e.g., polynucleotide variants, fragments and hybridizing sequences, encode polypeptides that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably
30 at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-

425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be
5 conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics
10 Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402
15 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for
20 nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments;
25 or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and
30 a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I

Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected
5 which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be
10 obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

15 As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed
20 mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically,
25 vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the
30 present invention, recursive sequence recombination, as described in U.S. Patent No.

5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as

provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

5 Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M
10 salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus,
15 hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

 According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted
20 inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to
25 their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-
30 32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288).

Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides
5 oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs
10 comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

15 Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m , binding energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or
20 prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the
25 OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997 Sep 1;25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic
30 domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*,

Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the
5 oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave
10 nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an
15 oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

20 Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close
25 proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and
30 cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an

RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically
5 incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the
10 ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can
15 be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be
20 administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles.
25 Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions
30 of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO

94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression
5 vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby.
10 Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA
15 vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, *Antisense Nucleic Acid Drug*
20 *Dev.* 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997
25 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, *Science*. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, *Bioorg Med Chem*. 1996 Jan;4(1):5-23). This chemistry has three important
5 consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

10 PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, *Bioorg Med Chem*. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of
15 closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this
20 difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

25 Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or
30 for specific functional requirements. Once synthesized, the identity of PNAs and their

derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

25 POLYNUCLEOTIDE IDENTIFICATION , CHARACTERIZATION AND EXPRESSION

Polynucleotides compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by

screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions
5 (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target
10 sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target
15 sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (e.g., *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will
20 dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

25 Any of a number of other template dependent processes, many of which are variations of the PCR™ amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No.
30 PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat.

Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a
5 nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other
10 amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is
15 screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by
20 nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are
25 selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may
30 involve generating a series of deletion clones. The resulting overlapping sequences can then be assembled into a single contiguous sequence. A full length cDNA molecule can be

generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res.* 5 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a 10 known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or 15 RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic.* 1:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids Res.* 19:3055-60, 1991). Other methods employing amplification may also be 20 employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs 25 may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct 30 expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of

the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous
5 in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring
10 sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For
15 example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

20 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be
25 engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al.
30 (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res.*

Symp. Ser. 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science* 269:202-204) and automated synthesis may be
5 achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.)
10 or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant
15 polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, i.e., a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well
20 known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) *Molecular Cloning, A*
25 *Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to,
30 microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid,

or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or
5 pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity.
10 Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In
15 mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be
20 selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence
25 encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion
30 proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose

beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

5 In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

 In cases where plant expression vectors are used, the expression of
10 sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J.*
15 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw
20 Hill, New York, N.Y.; pp. 191-185 and 187-196).

 An insect system may also be used to express a polypeptide of interest. For example, in one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a
25 non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed
30 (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or apt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a

marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates
5 expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include,
10 for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked
15 immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990;
20 Serological Methods, a Laboratory Manual, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med.* 158:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to
25 polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6
30 and labeled nucleotides. These procedures may be conducted using a variety of

commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be
5 cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the
10 encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow
15 purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to
20 facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase
25 cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using
30 solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated

synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

5

ANTIBODY COMPOSITIONS, FRAGMENTS THEREOF AND OTHER BINDING AGENTS

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant
10 or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunologically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

15 Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater
20 affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both
25 the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

30 An "antigen-binding site," or "binding portion" of an antibody refers to

the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as ovarian cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an

antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation
5 of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen
10 without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically.
15 Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J.*
20 *Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a
25 myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine,
30 aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture

supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab)₂" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V_H::V_L heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will

fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, e.g., U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a
5 light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and
10 "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (e.g., a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive
15 contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region.
20 Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a
25 binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize
30 the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) *Nature* 349:293-299; Lobuglio et al. (1989) *Proc. Nat. Acad. Sci. USA* 86:4220-4224; Shaw et al. (1987) *J Immunol.* 138:4534-4538; and Brown et al. (1987) *Cancer Res.* 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) *Nature* 332:323-327; Verhoeyen et al. (1988) *Science* 239:1534-1536; and Jones et al. (1986) *Nature* 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, e.g., a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) *Ann. Rev. Biochem.* 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (e.g., solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in *Sequences of Proteins of*

Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for
5 human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The
10 residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region
15 domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (e.g., electrostatic and hydrophobic)
20 contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect
25 mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives
30 thereof. Preferred radionuclides include ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi .

Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

5 A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-
10 containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A
15 linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional
20 or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

25 Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction
30 of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a

photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

5 It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be
10 coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides
15 such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative
20 radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

25

T CELLS COMPOSITIONS

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example,
30 T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone

marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or
5 unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a
10 tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell
15 specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the
20 proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7
25 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., *Current Protocols in Immunology*, vol. 1, Wiley Interscience (Greene 1998)). T
30 cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Tumor polypeptide-specific T

cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

15 PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and therapeutic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding

immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (e.g., U.S. Pat. No. 5,219,740; Miller and Rosman (1989) *BioTechniques* 7:980-990; Miller, A. D. (1990) *Human Gene Therapy* 1:5-14; Scarpa et al. (1991) *Virology* 180:849-852; Burns et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:8033-8037; and Boris-Lawrie and Temin (1993) *Cur. Opin. Genet. Develop.* 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) *J. Virol.* 57:267-274; Bett et al. (1993) *J. Virol.* 67:5911-5921; Mittereder et al. (1994) *Human Gene Therapy* 5:717-729; Seth et al. (1994) *J. Virol.* 68:933-940; Barr et al. (1994) *Gene Therapy* 1:51-58; Berkner, K. L. (1988) *BioTechniques* 6:616-629; and Rich et al. (1993) *Human Gene Therapy* 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, e.g., U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) *Molec. Cell. Biol.* 8:3988-3996; Vincent et al. (1990) *Vaccines* 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) *Current Opinion in Biotechnology* 3:533-539; Muzyczka, N. (1992) *Current Topics in Microbiol. and Immunol.* 158:97-129; Kotin, R. M. (1994) *Human Gene Therapy* 5:793-801; Shelling and Smith (1994) *Gene Therapy* 1:165-169; and Zhou et al. (1994) *J. Exp. Med.* 179:1867-1875.

Additional viral vectors useful for delivering the nucleic acid molecules encoding polypeptides of the present invention by gene transfer include those derived

from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK.sup.(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, e.g., Elroy-Stein and Moss, *Proc. Natl. Acad. Sci. USA* (1990) 87:6743-6747; Fuerst et al. *Proc. Natl. Acad. Sci. USA* (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described

above with respect to the production of vaccinia viruses. See, e.g., WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in
5 U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et
10 al. *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner
15 et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993;
20 and Guzman et al., *Cir. Res.* 73:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the
25 polynucleotide may be stably maintained in the cell as a separate, episomal segment of DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression
30 construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable
5 beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK)
10 and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device,
15 propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639
20 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances
25 or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins.
30 Certain adjuvants are commercially available as, for example, Freund's Incomplete

Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated
5 sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition
10 is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN- γ , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as
15 provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman,
20 *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL[®] adjuvants are available from Corixa Corporation (Seattle, WA; *see*, for example, US
25 Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by
30 Sato et al., *Science* 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila

Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example combinations of at least two of the following group comprising QS21, QS7, Quil A, β -escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamellar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol^R to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL[®] adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-MPL[®] adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 as disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

30

Additional illustrative adjuvants for use in the pharmaceutical

compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn®) (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula (I):
10 $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{-A-R}$

Wherein, n is 1-50, A is a bond or $-\text{C}(\text{O})-$, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein n is between 1 and 50, preferably 4-24, most preferably 9; the R component is C_{1-50} , preferably $\text{C}_4\text{-C}_{20}$ alkyl and most preferably C_{12} alkyl, and A is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12th edition: entry 7717). These adjuvant molecules are described in WO 99/52549.

The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified

to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med.* 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF α to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF α , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature"

cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997.

Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial,

intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release.

5 In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers

10 include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends

15 upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S.

20 Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems, such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No.

25 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins,

30 polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that

render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry

flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any
5 material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of
10 course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration,
15 product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash,
20 dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants.
25 Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which
30 are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as

free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain
5 a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that
10 easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable
15 oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be
20 preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution,
25 the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one
30 dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example,

"Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and

lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid
5 particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-
10 covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example, Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998 Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit,
15 Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions,
20 primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and
25 the like, into a variety of cultured cell lines and animals. Furthermore, the use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric
30 bilayer vesicles (also termed multilamellar vesicles (MLVs)).

Alternatively, in other embodiments, the invention provides for

pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric
5 overloading, such ultrafine particles (sized around 0.1 μ m) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

10

CANCER THERAPEUTIC METHODS

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of ovarian cancer. Within such methods, the pharmaceutical
15 compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical
20 removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

25 Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

30 Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established

tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews* 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be

introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

5 Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally.
10 Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune
15 response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or
20 partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

25 In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in
30 preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard

proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

CANCER DETECTION AND DIAGNOSTIC COMPOSITIONS, METHODS AND KITS

5 In general, a cancer may be detected in a patient based on the presence of one or more ovarian tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as ovarian cancer. In addition, such
10 proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a ovarian tumor sequence should be present at a level that is at
15 least three fold higher in tumor tissue than in normal tissue

 There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by
20 (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

 In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the
25 remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G,
30 protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized

binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length ovarian
5 tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane.
10 Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply
15 described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is
20 preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about
25 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the
30 binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an

aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay.

- 5 This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a
10 different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

- More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically
15 blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact
20 time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with ovarian cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve
25 equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

- Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second
30 antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed
5 and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a
10 different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as ovarian
15 cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that
20 is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot
25 of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered
30 positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In

general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of ovarian tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a ovarian tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10

nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the
5 diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold*
10 *Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules.
15 PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold
20 or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described
25 above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the
30 cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively,
5 polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein
10 markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components
15 necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as
20 reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least
25 one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

30 The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1Identification of Representative Ovarian Carcinoma cDNA Sequences

5

This Example illustrates the identification of ovarian tumor cDNA molecules.

Primary ovarian tumor and metastatic ovarian tumor cDNA libraries were each constructed in kanamycin resistant pZerO™-2 vector (Invitrogen) from pools of three different ovarian tumor RNA samples. For the primary ovarian tumor library, the following RNA samples were used: (1) a moderately differentiated papillary serous carcinoma of a 41 year old, (2) a stage IIIC ovarian tumor and (3) a papillary serous adenocarcinoma for a 50 year old caucasian. For the metastatic ovarian tumor library, the RNA samples used were omentum tissue from: (1) a metastatic poorly differentiated papillary adenocarcinoma with psammoma bodies in a 73 year old, (2) a metastatic poorly differentiated adenocarcinoma in a 74 year old and (3) a metastatic poorly differentiated papillary adenocarcinoma in a 68 year old.

The number of clones in each library was estimated by plating serial dilutions of unamplified libraries. Insert data were determined from 32 primary ovarian tumor clones and 32 metastatic ovarian tumor clones. The library characterization results are shown in Table I.

Table ICharacterization of cDNA Libraries

25

Library	# Clones in Library	Clones with Insert (%)	Insert Size Range (bp)	Ave. Insert Size (bp)
Primary Ovarian Tumor	1,258,000	97	175 - 8000	2356
Metastatic Ovarian Tumor	1,788,000	100	150 - 4300	1755

Four subtraction libraries were constructed in ampicillin resistant pcDNA3.1 vector (Invitrogen). Two of the libraries were from primary ovarian tumors and two were from metastatic ovarian tumors. In each case, the number of restriction

enzyme cuts within inserts was minimized to generate full length subtraction libraries. The subtractions were each done with slightly different protocols, as described in more detail below.

5 A. POTS 2 Library: Primary Ovarian Tumor Subtraction Library

Tracer: 10 µg primary ovarian tumor library, digested with Not I

Driver: 35 µg normal pancreas in pcDNA3.1(+)

20 µg normal PBMC in pcDNA3.1(+)

10 µg normal skin in pcDNA3.1(+)

10 35 µg normal bone marrow in pZErO™-2

Digested with Bam HI/Xho I/Sca I

Two hybridizations were performed, and Not I-cut pcDNA3.1(+) was the cloning vector for the subtracted library. Sequence results for previously unidentified clones that were randomly picked from the subtracted library are presented in Table II.

15

Table II
Ovarian Carcinoma Sequences

Sequence	SEQ ID NO
21909	2
21920	9
21921	10
25099	143
25101	144
25103	145
25107	146
25111	148
25113	149
25115	150
25116	151
25752	156
25757	158
25769	161
21907	1
21911	5
25763	160
25770	162

B. POTS 7 Library: Primary Ovarian Tumor Subtraction Library

Tracer: 10 µg primary ovarian tumor library, digested with Not I

Driver: 35 µg normal pancreas in pcDNA3.1(+)

20 µg normal PBMC in pcDNA3.1(+)

10 µg normal skin in pcDNA3.1(+)

35 µg normal bone marrow in pZErO™-2

Digested with Bam HI/Xho I/Sca I

~25 µg pZErO™-2, digested with Bam HI and Xho I

Two hybridizations were performed, and Not I-cut pcDNA3.1(+) was the
cloning vector for the subtracted library. Sequence results for previously unidentified
clones that were randomly picked from the subtracted library are presented in Table III.

Table III
Ovarian Carcinoma Sequences

Sequence	SEQ ID NO
24937	125
24940	128
24946	132
24950	133
24951	134
24956	137
25791	166
25796	167
25797	168
25804	171
24955	136

C. OS1D Library: Metastatic Ovarian Tumor Subtraction Library

Tracer: 10µg metastatic ovarian library in pZErO™-2, digested
with Not I

Driver: 24.5µg normal pancreas in pcDNA3.1

14µg normal PBMC in pcDNA3.1

14µg normal skin in pcDNA3.1

24.5µg normal bone marrow in pZErO™-2

50µg pZErO™-2, digested with Bam HI/Xho I/Sfu I

Three hybridizations were performed, and the last two hybridizations were done with an additional 15µg of biotinylated pZErO™-2 to remove contaminating pZErO™-2 vectors. The cloning vector for the subtracted library was pcDNA3.1/Not I cut. Sequence results for previously unidentified clones that were randomly picked from the subtracted library are presented in Table IV.

Table IV
Ovarian Carcinoma Sequences

Sequence	SEQ ID NO
24635	57
24647	63
24661	69
24663	70
24664	71
24670	72
24675	75
23645.1	13
23660.1	16
23666.1	19
23679.1	23
24651	65
24683	78

10

D. OS1F Library: Metastatic Ovarian Tumor Subtraction Library

Tracer: 10µg metastatic ovarian tumor library, digested with Not

15 I

Driver: 12.8µg normal pancreas in pcDNA3.1
 7.3µg normal PBMC in pcDNA3.1
 7.3µg normal skin in pcDNA3.1
 12.8µg normal bone marrow in pZErO™-2
 25µg pZErO™-2, digested with Bam HI/Xho I/Sfu I

20

One hybridization was performed. The cloning vector for the subtracted library was pcDNA3.1/Not I cut. Sequence results for previously unidentified clones that were randomly picked from the subtracted library are presented in Table V.

Table V
Ovarian Carcinoma Sequences

Sequence	SEQ ID NO
24344	33
24356	42
24368	53
24696	86
24699	89
24701	90
24703	91
24707	95
24709	97
24732	111
24745	120
24746	121
24337	28
24348	35
24351	38
24358	44
24360	46
24361	47
24690	81
24692	82
24694	84
24705	93
24711	98
24713	99
24727	107
24741	117
24359 (78% Human mRNA for KIAA0111 gene, complete cds)	45
24336 (79% with H. sapiens mitochondrial genome (consensus sequence))	27
24737 (84% Human ADP/ATP translocase mRNA)	114
24363 (87% Homo sapiens eukaryotic translation elongation factor 1 alpha 1 (EEF1A1))	49
24357 (87% S. scrofa mRNA for UDP glucose pyrophosphorylase)	43
24362 (88% Homo sapiens Chromosome 16 BAC clone CIT987SK-A-233A7)	48
24704 (88% Homo sapiens chromosome 9, clone hRPK.401_G_18)	92
24367 (89% Homo sapiens 12p13.3 BAC	52

Sequence	SEQ ID NO
RCPII1-935C2)	
24717 (89% Homo sapiens proliferation-associated gene A (natural killer-enhancing factor A) (PAGA)	103
24364 (89% Human DNA sequence from PAC 27K14 on chromosome Xp11.3-Xp11.4)	50
24355 (91% Homo sapiens chromosome 17, clone hCIT.91_J_4)	41
24341 (91% Homo sapiens chromosome 5, BAC clone 249h5 (LBNL H149)	32
24714 (91% Human DNA sequence from clone 125N5 on chromosome 6q26-27)	100

The sequences in Table VI, which correspond to known sequences, were also identified in the above libraries.

5

Table VI
Ovarian Carcinoma Sequences

Identity	SEQ ID NO	Sequence	Library
Genomic sequence from Human 9q34	56	24634	OS1D
Homo sapiens 12p13.3 PAC RPCI1-96H9 (Roswell Park Cancer Institute Human PACLibrary)	66	24653	OS1D
Homo sapiens annexin II (lipocortin II) (ANX2) mRNA	60	24640	OS1D
Homo sapiens eukaryotic translation elongation factor 1 alpha 1 (EEF1A1)	55	24627	OS1D
Homo sapiens ferritin, heavy polypeptide 1 (FTH1)	64	24648	OS1D
Homo sapiens FK506-binding protein 1A (12kD) (FKBP1A) mRNA	22	23677.1	OS1D
Homo sapiens growth arrest specific transcript 5 gene	73	24671	OS1D
Homo sapiens keratin 18 (KRT18) mRNA	68	24657	OS1D
Homo sapiens mRNA; cDNA DKFZp564H182	76	24677	OS1D
Homo sapiens ribosomal protein S7 (RPS7)	74	24673	OS1D
Homo sapiens ribosomal protein, large, P0 (RPLP0) mRNA	14	23647.1	OS1D
Homo sapiens T cell-specific tyrosine kinase mRNA	67	24655	OS1D
Homo sapiens tubulin, alpha, ubiquitous (K-ALPHA-1)	61	24642	OS1D
HSU78095 Homo sapiens placental bikunin mRNA	18	23662.1	OS1D
Human BAC clone GS055K18 from 7p15-p21	11	23636.1	OS1D

Identity	SEQ ID NO	Sequence	Library
Human insulin-like growth factor-binding protein-3 gene	58	24636	OS1D
Human mRNA for ribosomal protein	79	24687	OS1D
Human non-histone chromosomal protein HMG-14 mRNA	62	24645	OS1D
Human ribosomal protein L3 mRNA, 3' end	59	24638	OS1D
Human TSC-22 protein mRNA	77	24679	OS1D
HUMGFIBPA Human growth hormone-dependent insulin-like growth factor-binding protein	12	23637.1	OS1D
HUMMTA Homo sapiens mitochondrial DNA	17	23661.1	OS1D
HUMMTCG Human mitochondrion	21	23673.1	OS1D
HUMTI227HC Human mRNA for TI-227H	20	23669.1	OS1D
HUMTRPM2A Human TRPM-2 mRNA	15	23657.1	OS1D
Genomic sequence from Human 13	80	24689	OS1F
H.sapiens CpG island DNA genomic MseI fragment, clone 84a5	104	24719	OS1F
H.sapiens RNA for snRNP protein B	110	24730	OS1F
Homo sapiens (clone L6) E-cadherin (CDH1) gene	108	24728	OS1F
Homo sapiens atrophin-1 interacting protein 4 (AIP4) mRNA	37	24350	OS1F
Homo sapiens CGI-08 protein mRNA	102	24716	OS1F
Homo sapiens clone 24452 mRNA sequence	54	24374	OS1F
Homo sapiens clone IMAGE 286356	83	24693	OS1F
Homo sapiens cornichon protein mRNA	113	24735	OS1F
Homo sapiens hypothetical 43.2 Kd protein mRNA	87	24697	OS1F
Homo sapiens interleukin 1 receptor accessory protein (IL1RAP) mRNA.	29	24338	OS1F
Homo sapiens K-Cl cotransporter KCC4 mRNA, complete cds	31	24340	OS1F
Homo sapiens keratin 8 (KRT8) mRNA	115	24739	OS1F
Homo sapiens mRNA for DEPP (decidual protein induced by progesterone)	36	24349	OS1F
Homo sapiens mRNA for KIAA0287 gene	101	24715	OS1F
Homo sapiens mRNA for KIAA0762 protein	118	24742	OS1F
Homo sapiens mRNA for zinc-finger DNA-binding protein, complete cds	24	24333	OS1F
Homo sapiens mRNA; cDNA DKFZp434K114	112	24734	OS1F
Homo sapiens mRNA; cDNA DKFZp564E1962 (from clone DKFZp564E1962)	25	24334	OS1F
Homo sapiens nuclear chloride ion channel protein (NCC27) mRNA	34	24345	OS1F
Homo sapiens ribosomal protein L13 (RPL13)	109	24729	OS1F
Homo sapiens senescence-associated epithelial	94	24706	OS1F

Identity	SEQ ID NO	Sequence	Library
membrane protein (SEMP1)			
Homo sapiens tumor protein, translationally-controlled 1 (TPT1) mRNA.	26	24335	OS1F
Homo sapiens tumor suppressing subtransferable candidate 1 (TSSC1)	51	24366	OS1F
Homo sapiens v-fos FBJ murine osteosarcoma viral oncogene homolog(FOS) mRNA	85	24695	OS1F
Homo sapiens zinc finger protein slug (SLUG) gene	106	24722	OS1F
Human clone 23722 mRNA	105	24721	OS1F
Human clones 23667 and 23775 zinc finger protein mRNA	119	24744	OS1F
Human collagenase type IV mRNA, 3' end.	39	24352	OS1F
Human DNA sequence from PAC 29K1 on chromosome 6p21.3-22.2.	116	24740	OS1F
Human ferritin H chain mRNA	96	24708	OS1F
Human heat shock protein 27 (HSPB1) gene exons 1-3	88	24698	OS1F
Human mRNA for KIAA0026 gene	30	24339	OS1F
Human mRNA for T-cell cyclophilin	40	24354	OS1F
Genomic sequence from Human 9q34, complete sequence [Homo sapiens]	140	25092	POTS2
H.sapiens DNA for muscle nicotinic acetylcholine receptor gene promotor, clone ICRFc105F02104	3	21910	POTS2
Homo sapiens breast cancer suppressor candidate 1 (bcscl) mRNA, complete cds	142	25098	POTS2
Homo sapiens CGI-151 protein mRNA, complete cds	8	21916	POTS2
Homo sapiens complement component 3 (C3) gene, exons 1-30.	4	21913	POTS2
Homo sapiens mRNA for hepatocyte growth factor activator inhibitor type 2, complete cds	159	25758	POTS2
Homo sapiens preferentially expressed antigen of melanoma (PRAME) mRNA	153	25745	POTS2
Homo sapiens prepro dipeptidyl peptidase I (DPP-I) gene, complete cds	152	25117	POTS2
Homo sapiens SKB1 (S. cerevisiae) homolog (SKB1) mRNA.	147	25110	POTS2
Homo sapiens SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4)	6	21914	POTS2
Human 12S RNA induced by poly(rI), poly(rC) and Newcastle disease virus	155	25749	POTS2
Human ferritin Heavy subunit mRNA, complete cds.	7	21915	POTS2
Human glyceraldehyde-3-phosphate dehydrogenase	141	25093	POTS2

Identity	SEQ ID NO	Sequence	Library
(GAPDH) mRNA, complete cds.			
Human mRNA for fibronectin (FN precursor)	157	25755	POTS2
Human translocated t(8;14) c-myc (MYC) oncogene, exon 3 and complete cds	154	25746	POTS2
H.sapiens vegf gene, 3'UTR	169	25799	POTS7
Homo sapiens 30S ribosomal protein S7 homolog mRNA, complete cds	170	25802	POTS7
Homo sapiens acetyl-Coenzyme A acetyltransferase 2 (acetoacetyl Coenzyme A thiolase) (ACAT2) mRNA	172	25808	POTS7
Homo sapiens amyloid beta precursor protein-binding protein 1, 59kD (APPBP1) mRNA.	138	24959	POTS7
Homo sapiens arylacetamide deacetylase (esterase) (AADAC) mRNA.	129	24942	POTS7
Homo sapiens clone 23942 alpha enolase mRNA, partial cds	165	25787	POTS7
Homo sapiens echinoderm microtubule-associated protein-like EMAP2 mRNA, complete cds	130	24943	POTS7
Homo sapiens IMP (inosine monophosphate) dehydrogenase 2 (IMPDH2) mRNA	164	25775	POTS7
Homo sapiens megakaryocyte potentiating factor (MPF) mRNA.	126	24938	POTS7
Homo sapiens mRNA for KIAA0552 protein, complete cds	163	25771	POTS7
Homo sapiens Norrie disease protein (NDP) mRNA	173	25809	POTS7
Homo sapiens podocalyxin-like (PODXL) mRNA.	131	24944	POTS7
Homo sapiens synaptogyrin 2 (SYNGR2) mRNA.	135	24952	POTS7
Human aldose reductase mRNA, complete cds.	139	24969	POTS7
Human cyclooxygenase-1 (PTSG1) mRNA, partial cds	124	24935	POTS7
Human H19 RNA gene, complete cds.	122	24933	POTS7
Human mRNA for Apo1_Human (MER5(Aop1-Mouse)-like protein), complete cds	127	24939	POTS7
Human triosephosphate isomerase mRNA, complete cds.	123	24934	POTS7

Still further ovarian carcinoma polynucleotide and/or polypeptide sequences identified from the above libraries are provided below in Table VII.

- 5 Sequences O574S (SEQ ID NOs: 183 & 185), O584S (SEQ ID NO: 193) and O585S (SEQ ID NO: 194) represent novel sequences. The remaining sequences exhibited at least some homology with known genomic and/or EST sequences.

Table VII

SEQ ID:	Sequence	Library
174 :	O565S_CRABP	OS1D
175 :	O566S_Ceruloplasmin	POTS2
176 :	O567S_41191.SEQ(1>487)	POTS2
177 :	O568S_KIAA0762.seq(1>3999)	POTS7
178 :	O569S_41220.seq(1>1069)	POTS7
179 :	O570S_41215.seq(1>1817)	POTS2
180:	O571S_41213.seq(1>2382)	POTS2
181 :	O572S_41208.seq(1>2377)	POTS2
182 :	O573S_41177.seq(1>1370)	OS1F
183 :	O574S_47807.seq(1>2060)	n/a
184 :	O568S/VSGF DNA seq	n/a
185:	O574S_47807.seq(1>3000)	n/a
186:	O568S/VSGF protein seq	n/a
187 :	449H1(57581)	OS1D
188:	451E12(57582)	OS1D
189 :	453C7_3'(57583.1)Osteonectin	OS1D
190 :	453C7_5'(57583.2)	OS1D
191:	456G1_3'(57584.1)Neurotensin	OS1F
192:	456G1_5'(57584.2)	OS1F
193:	O584S_465G5(57585)	OS1F
194:	O585S_469B12(57586)	POTS2
195:	O569S_474C3(57587)	POTS7
196:	483B1_3'(24934.1)Triosephosphate	POTS7
197:	57885 Human preferentially expressed antigen of melanoma	POTS2
198:	57886 Chromosome 22q12.1 clone CTA-723E4	POTS2
199:	57887 Homologous to mouse brain cDNA clone MNCb-0671	POTS2

5 From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. An isolated polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) polynucleotides recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193, 194; and

(b) complements of the foregoing polynucleotides.

2. A polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) polynucleotides recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193, 194; and

(b) complements of such polynucleotides.

3. An isolated polynucleotide encoding at least 5 amino acid residues of a polypeptide according to claim polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian

carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (a) polynucleotides recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 57, 63, 65, 69-72, 75, 78, 81, 82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 143-146, 148-151, 156, 158, 160-162, 166-168 or 171, 174-183, 185, 193, 194; and
- (b) complements of the foregoing polynucleotides

4. A polynucleotide according to claim 3, wherein the polynucleotide encodes an immunogenic portion of the polypeptide.

5. A polynucleotide according to claim 3, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 57, 63, 65, 69-72, 75, 78, 81, 82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 143-146, 148-151, 156, 158, 160-162, 166-168, 171 or 174-183, 185, 193, 194 or a complement of any of the foregoing sequences.

6. An isolated polynucleotide complementary to a polynucleotide according to claim 3.

7. An expression vector comprising a polynucleotide according to claim 3 or claim 6.

8. A host cell transformed or transfected with an expression vector according to claim 7.

9. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.

10. A pharmaceutical composition according to claim 9, wherein the polypeptide comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193 and 194.

11. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.

12. A vaccine according to claim 11, wherein the polypeptide comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193 and 194.

13. A pharmaceutical composition comprising:

(a) a polynucleotide encoding an ovarian carcinoma polypeptide, wherein the polypeptide comprises at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-

82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193, 194; and

- (ii) complements of the foregoing polynucleotides; and
- (b) a physiologically acceptable carrier.

14. A pharmaceutical composition according to claim 13, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193, 194 or a complement of any of the foregoing sequences.

15. A vaccine comprising:

(a) a polynucleotide encoding an ovarian carcinoma polypeptide, wherein the polypeptide comprises at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (i) polynucleotides recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193, 194; and
- (ii) complements of the foregoing polynucleotides; and

16. A vaccine according to claim 15, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-

100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193, 194.

17. A pharmaceutical composition comprising:

(a) an antibody that specifically binds to an ovarian carcinoma protein, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1, 2, 5, 9, 10, 13, 16, 19, 23, 27, 28, 32, 33, 35, 38, 41-50, 52, 53, 56, 57, 63, 65, 69-72, 75, 78, 80-82, 84, 86, 89-93, 95, 97-100, 103, 107, 111, 114, 117, 120, 121, 125, 128, 132-134, 136, 137, 140, 143-146, 148-151, 156, 158, 160-162, 166-168, 171, 174-183, 185, 193, 194; and

(ii) complements of such polynucleotides; and

(b) a physiologically acceptable carrier.

18. A method for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient an effective amount of an agent selected from the group consisting of:

(a) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

(ii) complements of such polynucleotides;

(b) a polynucleotide encoding a polypeptide as recited in (a); and

(c) an antibody that specifically binds to an ovarian carcinoma protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

(ii) complements of such polynucleotides;
and thereby inhibiting the development of ovarian cancer in the patient.

19. A method according to claim 18, wherein the agent is present within a pharmaceutical composition according to any one of claims 9, 13 or 17.

20. A method according to claim 18, wherein the agent is present within a vaccine according to any one of claims 11, 15 or 18.

21. A fusion protein comprising at least one polypeptide according to claim 1.

22. A polynucleotide encoding a fusion protein according to claim 21.

23. A pharmaceutical composition comprising a fusion protein according to claim 21 in combination with a physiologically acceptable carrier.

24. A vaccine comprising a fusion protein according to claim 21 in combination with a non-specific immune response enhancer.

25. A pharmaceutical composition comprising a polynucleotide according to claim 22 in combination with a physiologically acceptable carrier.

26. A vaccine comprising a polynucleotide according to claim 22 in combination with a non-specific immune response enhancer.

27. A method for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 23 or claim 25.

28. A method for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 23 or claim 26.

29. A pharmaceutical composition, comprising:

(a) an antigen presenting cell that expresses an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

(ii) complements of such polynucleotides; and

(b) a pharmaceutically acceptable carrier or excipient.

30. A vaccine, comprising:

(a) an antigen presenting cell that expresses an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not

substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
 - (ii) complements of such polynucleotides; and
- (b) a non-specific immune response enhancer.

31. A vaccine comprising:

- (a) an anti-idiotypic antibody or antigen-binding fragment thereof that is specifically bound by an antibody that specifically binds to an ovarian carcinoma protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
 - (ii) complements of such polynucleotides; and
- (b) non-specific immune response enhancer.

32. A vaccine according to claim 30 or claim 31, wherein the immune response enhancer is an adjuvant.

33. A pharmaceutical composition, comprising:

- (a) a T cell that specifically reacts with an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

- (ii) complements of such polynucleotides; and
(b) a physiologically acceptable carrier.

34. A vaccine, comprising:

(a) a T cell that specifically reacts with an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199 and

- (ii) complements of such polynucleotides; and
(b) a non-specific immune response enhancer.

35. A method for inhibiting the development of ovarian cancer in a patient, comprising administering to the patient an effective amount of a pharmaceutical composition according to claim 29 or claim 33.

36. A method for inhibiting the development of ovarian cancer in a patient, comprising administering to the patient an effective amount of a vaccine according to any one of claims 30, 31 or 34.

37. A method for stimulating and/or expanding T cells, comprising contacting T cells with:

(a) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
 - (ii) complements of such polynucleotides;
- (b) a polynucleotide encoding such a polypeptide; and/or
- (c) an antigen presenting cell that expresses such a polypeptide under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

38. A method according to claim 37, wherein the T cells are cloned prior to expansion.

39. A method for stimulating and/or expanding T cells in a mammal, comprising administering to a mammal a pharmaceutical composition comprising:

- (a) one or more of:
 - (i) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
complements of such polynucleotides;

- (ii) a polynucleotide encoding an ovarian carcinoma polypeptide;

or

(iii) an antigen-presenting cell that expresses an ovarian carcinoma polypeptide; and

(b) a physiologically acceptable carrier or excipient;
and thereby stimulating and/or expanding T cells in a mammal.

40. A method for stimulating and/or expanding T cells in a mammal, comprising administering to a mammal a vaccine comprising:

(a) one or more of:

(i) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
complements of such polynucleotides;

(ii) a polynucleotide encoding an ovarian carcinoma polypeptide;

or

(iii) an antigen-presenting cell that expresses an ovarian carcinoma polypeptide; and

(b) a non-specific immune response enhancer;
and thereby stimulating and/or expanding T cells in a mammal.

41. A method for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient T cells prepared according to the method of claim 39 or claim 40.

42. A method for inhibiting the development of ovarian cancer in a patient, comprising the steps of:

- (a) incubating CD4⁺ T cells isolated from a patient with one or more of:
 - (i) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
 - polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
 - complements of such polynucleotides;
 - (ii) a polynucleotide encoding an ovarian carcinoma polypeptide;
- or
- (iii) an antigen-presenting cell that expresses an ovarian carcinoma polypeptide;
 - such that T cells proliferate; and
- (b) administering to the patient an effective amount of the proliferated T cells, and therefrom inhibiting the development of ovarian cancer in the patient.

43. A method for inhibiting the development of ovarian cancer in a patient, comprising the steps of:

- (a) incubating CD4⁺ T cells isolated from a patient with one or more of:
 - (i) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
 - polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
 - complements of such polynucleotides;

- (ii) a polynucleotide encoding an ovarian carcinoma polypeptide;
 - or
 - (iii) an antigen-presenting cell that expresses an ovarian carcinoma polypeptide;
- such that T cells proliferate;
- (b) cloning one or more proliferated cells; and
 - (c) administering to the patient an effective amount of the cloned T cells.

44. A method for inhibiting the development of ovarian cancer in a patient, comprising the steps of:

- (a) incubating CD8⁺ T cells isolated from a patient with one or more of:
 - (i) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
 - polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
 - complements of such polynucleotides;
 - (ii) a polynucleotide encoding an ovarian carcinoma polypeptide;
 - or
 - (iii) an antigen-presenting cell that expresses an ovarian carcinoma polypeptide;
- such that T cells proliferate; and
- (b) administering to the patient an effective amount of the proliferated T cells, and therefrom inhibiting the development of ovarian cancer in the patient.

45. A method for inhibiting the development of ovarian cancer in a patient, comprising the steps of:

(a) incubating CD8⁺ T cells isolated from a patient with one or more of:

(i) an ovarian carcinoma polypeptide comprising at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
complements of such polynucleotides;

(ii) a polynucleotide encoding an ovarian carcinoma polypeptide;

or

(iii) an antigen-presenting cell that expresses an ovarian carcinoma polypeptide;

such that the T cells proliferate;

(b) cloning one or more proliferated cells ; and

(c) administering to the patient an effective amount of the cloned
T cells.

46. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to an ovarian carcinoma protein, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and
187-199; and

(ii) complements of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

47. A method according to claim 46, wherein the binding agent is an antibody.

48. A method according to claim 47, wherein the antibody is a monoclonal antibody.

49. A method according to claim 46, wherein the cancer is ovarian cancer.

50. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to an ovarian carcinoma protein, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

(ii) complements of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

51. A method according to claim 50, wherein the binding agent is an antibody.

52. A method according to claim 51, wherein the antibody is a monoclonal antibody.

53. A method according to claim 50, wherein the cancer is ovarian cancer.

54. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes an ovarian carcinoma protein, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

(ii) complements of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

55. A method according to claim 54, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

56. A method according to claim 54, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

57. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes an ovarian carcinoma protein, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

(ii) complements of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

58. A method according to claim 57, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

59. A method according to claim 57, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

60. A diagnostic kit, comprising:

(a) one or more antibodies or antigen-binding fragments thereof that specifically bind to an ovarian carcinoma protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and

(ii) complements of the foregoing polynucleotides.; and

(b) a detection reagent comprising a reporter group.

61. A kit according to claim 60, wherein the antibodies are immobilized on a solid support.

62. A kit according to claim 61, wherein the solid support comprises nitrocellulose, latex or a plastic material.

63. A kit according to claim 60, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

64. A kit according to claim 60, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

65. A diagnostic kit, comprising:

(a) an oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes an ovarian

carcinoma protein, wherein the ovarian carcinoma protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (i) polynucleotides recited in any one of SEQ ID NOs:1-185 and 187-199; and
 - (ii) complements of the foregoing polynucleotides; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

SEQUENCE LISTING

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 Xu, Jiangchun
 Stolk, John A.

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atctcgggcc	ctcctcttca	ggaatcttcc	tgaagacatg	gcccagtcga	aggcccagga	300

```

tggtttttgc tgcggccccc tggggtagga gggacagaga gacagggaga gtcagcctcc 360
acattcagag gcatacacaag taatggcaca attctt 396

```

```

<210> 13
<211> 396
<212> DNA
<213> Homo sapien

```

```

<400> 13
accacaggct ggccacaaga agcgcctggag tgtgctggcg gctgcaggcc tacggggcct 60
ggtcgggctg ctgcacgtgc gtgccggcct ctgctgcggg gtcacccgag cccacaagaa 120
ggccatcgcc accctgtgct tcagccccgc ccacgagacc catctcttca cggcctccta 180
tgacaagcgg atcatcctct gggacatcgg ggtgcccaac caggactacg aattccaggc 240
cagccagctg ctcacactgg acaccacctc tatccccctg cgctctgccc ctgtcgctc 300
ctgcccggac gcccgctgc tggccgggct cgagggcggc tgctgctgct gggacgtgcg 360
gctggaccag ccccaaaaga ggaggggtgtg tgaagt 396

```

```

<210> 14
<211> 396
<212> DNA
<213> Homo sapien

```

```

<400> 14
acggcgctct cgtggaagtg acatcgtctt taaacctgc gtggcaatcc ctgacgcacc 60
gccgtgatgc ccagggaaga cagggcgacc tggaagtcca actacttcct taagatcatc 120
caactattgg atgattatcc gaaatgtttc attgtgggag cagacaatgt gggctccaag 180
cagatgcagc agatccgcat gtcccttcgc gggaaggctg tgggtgctgat gggcaagaac 240
accatgatgc gcaaggccat ccgagggcac ctggaaaaca acccagctct ggagaaactg 300
ctgcctcata tccgggggaa tgtgggcttt gtgttcacca aggaggacct cactgagatc 360
agggacatgt tgctggccaa taaggtgcc a gctgct 396

```

```

<210> 15
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 15
accgcgcggg cacagggtgc cgctgaccga ggctgcaaaa gactccagaa ttggaggcat 60
gatgaagact ctgctgctgt ttgtggggct gctgctgacc tgggagagtg ggcaggtcct 120
gggggaccag acggtctcag acaatgagct ccaggaaatg tccaatcagg gaagtaagta 180
cgtcaataag gaaattcaaa atgcttgta acggggtgaa acagataaag actctcatag 240
aaaaaaciaa cgaagagcgc aagacactgc tcagcaacct agaagaagcc aagaagaaga 300
aagaggatgc cctaaatgag accagggaaat canagacaaa gctgaaggag ctcccaggag 360
tgtgcaatga gaccatgatg gccctctggg aagagt 396

```

```

<210> 16
<211> 396
<212> DNA
<213> Homo sapien

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

<400> 16
tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttngggggg 120
nnnaaanttt tttntnanan nnnngggnaa aaaaaaaaaa aanaangggg gnnntnnggc 180
ccnnnanaaa aaaanngnna annaancccc ccnnnnnnnc ccncnnntnn ggaaananna 240
aaaccccccc cngggngggg nnaaaaaannc ccnggggnan tttttatnnn annccccccc 300
ccnggggggg gngggaaaaa aaaantnccc ccnannaana nnggggnccc ccntttttnc 360
aaaanggggg nccgggcccc ccnnantntt nggggg 396

<210> 17
<211> 396
<212> DNA
<213> Homo sapien

<400> 17
accacactaa ccatatacca atgatggcgc gatgtaacac gagaaagcac ataccaaggc 60
caccacacac cacctgtcca aaaaggcctt cgatacggga taatcctatt tattacctca 120
gaagtttttt tcttcgcagg atttttctga gccttttacc actccagcct agccccctacc 180
ccccaaactag gagggcactg gcccccaaca ggcattcacc cgctaaatcc cctagaagtc 240
ccactcctaa acacatccgt attactcgca tcaggagtat caatcacctg agctcaccat 300
agtctaataa aaaacaaccg aaaccaata attcaagcac tgcttattac aattttactg 360
ggtctctatt ttacctcct acaagcctca gaggac 396

<210> 18
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

<400> 18
tttttttttt tttttttttt tttttttttt tttttttttt ttttttttta ntcnaaaggg 60
gaaggncctt ttttattaaa nttggncatt ttacttttct tttttnaaaa ngctaanaaa 120
aaanttttnt ttntncttaa aaaaaccctn natntcacna ncaaaaaaaaa cnatccccc 180
ntnctttttg tgataaaaaa aaaggcaatg gaattcaacn tancctaana aaacttttnc 240
tgaggaggaa aaaaatttnt ccgngggaaa cacttggggc tntccaaant gnanccatnc 300
tangaggacc ntctntaaga tttccaaang aaacccttcc ctnccaaang nantaccccg 360
ntgcctacnn ccataaaaaa aaacctcanc cntaan 396

<210> 19
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)

<223> n = A,T,C or G

<400> 19

tttttttttt	tttttttttt	tttttttttt	tttttttttt	ttttttntgg	tctgggcttt	60
tattttacna	aaaancta	an	gnnaaanntn	cnttaaaacta	antngaana	120
ngaaaaaggn	ctgggggnnt	cntttacaaa	aanggnncngg	gncaantttg	ggcttaaaan	180
ttcaaaaagg	gnncntcaaa	ngggtttgca	tttgcatgtt	tcancnctaa	ancgnangaa	240
naaaccngg	ngncncctgg	gaaaagttnt	tnancntcca	aaanatnaan	ntttgnanc	300
agggntttt	tgggnaaaaa	aannanttcc	anaaactttc	catcccctgg	ntttgggttc	360
ggccttgngt	tttcgggnatn	atntccntta	angggg			396

<210> 20

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 20

tttttttttt	tttttttttt	ttttttctna	acaaaccctg	ttnttgggng	ggngngggta	60
taatactaag	ttganatgat	ntcatttacg	ggggaaggcn	ctttgtgaan	naggccttat	120
ttctnttgnc	ctttcgtaca	gggaggaatt	tgaagtaaan	anaaacnac	ctggattact	180
ccggtctgaa	ctcaaatac	gtaggacttt	aatcgttgaa	caaacaaacc	tttaatatagc	240
gctgcncat	tgggatgtcc	tgatccaaca	tcgaggncgt	aaaccctatt	gttgatatgg	300
actctaaaaa	taggattgcg	ctgttatccc	tagggtaact	tgttcccgtg	gtcaaagtta	360
ttggatcaat	tgagtataag	tagttcgctt	tgactg			396

<210> 21

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 21

acatanatnt	tatactanca	ttnacatct	cacttgnagg	aanactanta	tatcnctcac	60
acctnatatc	ctnctacta	tgctagaag	gaataatact	atngctgttn	attatancta	120
ctntnataac	cctnaacacc	cactccctct	tanccaatat	tgtgcctatt	gccatactag	180
tnnttgccgc	ctgnaagca	gnngngggcc	tanccntact	agnctcaatc	tccaacacnt	240
atggcctana	ctacgtacat	aacctaaacc	tactcnaatg	ctaaaactaa	tcnncccaac	300
anttatntta	ctaccactga	catgactttc	caaaaaacac	atantttgaa	tcaacncanc	360
caccacacanc	ctanttatta	ncatcatccc	cntact			396

<210> 22

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 22
 tttttttttt ttttganaaa agccggcata aagcactttt attgcaataa taaaacttga 60
 gactcataaa tgggtgctggg ggaaggggtgc agcaacgatt tctcaccaaa tctactacaca 120
 ggacagcaaa ggggtgagaa ggggctgagg gaggaaaagc caggaaactg agatcagcag 180
 agggagccaa gcatcaaaaa acaggagatg ctgaagctgc gatgaccagc atcattttct 240
 taanagaaca ttcaaggatt tgtcatgatg gctgggcttt cactgggtgt taagtctaca 300
 aacagcacct tcaattgaaa ctgtcaatta aagttcttaa gatttaggaa gtgggtggagc 360
 ttggaaagtt atgagattac aaaattcctg aaagtc 396

<210> 23
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 23
 acaaaggcgg ttccaagcta aggaattcca tcagtgtttt tttcgcagcc accaaattta 60
 gcaggcctgt gaggttttca tatcctgaag agatgtattt taaagctttt tttttttaat 120
 gaaaaaatgt cagacacaca caaaagtaga atagtaccat ggagtcccca cgtaccacagc 180
 ctgcagcttc aacagttacc acatttgcca accggagaga ctgccaaggc aggaaaaagc 240
 cctggaaaagc ccacggcccc tttttccctt gggtcagagg ccttagagct ggctgccaaa 300
 gcagccaacc aaaggggcag ctcagctcct tcgtggcacc agcagtgttc ctgatgcagt 360
 tgaagagttg atgtctttga caacatacgg acactg 396

<210> 24
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 24
 cgactatcct ctcagattct tatctggcac taatttataa ctattatatt atcagagact 60
 atgtagcaat atatcagtgc acaggcgcac ccaggcctg tacagatgta tgtctacacg 120
 taagtataaa tgaatttgca taccaggttt tacacttgca tctctaatag agattaaaaa 180
 caacaaattg gcctcttcct aagtatatta atatcattta tccttacatt ttatgcctcc 240
 ccctaaatta atgactgagt tgggtgaaaag cggctaggtt ttattcatac tgttttttgt 300
 tctcaacttc aanagtaatc tacctctgaa aaatttntan tttaatattn nnnnnnagga 360
 atttgngcca ctttannnct tncnntntnn tnnccn 396

<210> 25
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

```

<400> 25
tttttttttt tttttttttt gtctttttaa aaatataaaa gtgttattat tttaaaacat    60
caagcattac agactgtaaa atcaattaan aactttctgt atatgaggac aaaaatacat    120
ttaanacata tacaanaaga tgctttttcc tgagtagaat gcaaactttt atattaagct    180
tctttgaatt ttcaaaatgt aaaataccaa ggctttttca catcagacaa aaatcaggaa    240
tggtcacctt cacatccaaa aagaaaaaaa aaaaaaanc aattttcaag ttgaagttna    300
ncaanaatga tgtaaaatct gaaaaaagtg gccaaaattt taanttncaa canannngnn    360
ncagnttttn tggatctn tn nnnnnncttc nnntnn

```

```

<210> 26
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 26
gacgtcccc cctccccccg agcgccgctc cggtgcacc gcgctcgctc cgagtttcag    60
gtcgtgcta agctagcgcc gtcgtcgtct cccttcagtc gccatcatga ttatctaccg    120
ggacctcatc agccacgatg agatgttctc cgacatctac aagatccggg agatcgcgga    180
cgggttgtgc ctggagggtg aggggaagat ggtcagtagg acagaaggta acattgatga    240
ctcgtcatt ggtggaaatg cctccgctga agggcccgag ggcgaaggta cccgaaagca    300
cagtaatcac tgnngncnat nttgtcatga accatcacct gcnngaagca annttnacaa    360
aanaancctn cnnnnannnc ctnnnnnatt ncnnnn

```

```

<210> 27
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 27
tttttttttt tttttttttt tttttttttt tttttttttt tggctaaant ttatgtatac    60
nggttnttca aangnggggg aggggggggg gcatccatnt annncncca ggtttatggn    120
gggntntnt actattanna ntttctnctt caaancaag gnttntcaaa tcatnaaaat    180
tattaanatt ncngctgnta aaaaaangaa tgaaccnncn nanganagga nntttcatgg    240
ggggnatgca tcggggnann ccnaanaacc ncggggccat tcccganagg cccaaaaaat    300
gtttnnnnaa aaagggtaaa nttaccccn tnaantttat annnnaaann nnannnnagc    360
ccaannnttn nnnnnnnnnn nnnccnnna nnnnnn

```

```

<210> 28
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

```

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 28

```
cgaccttttt tttttttttt atagatgaaa gagggtttat ttattaatat atgatagcct      60
tggtcctaaaa aagacaaatg agggctcaaa aaggaattac agtaacttta aaaaatatat      120
taaacatatac caagatccta aatatattat tctcccaaaa agctagctgc ttccaaactt      180
gatttgatat tttgcatggt ttcctacgt tgcttggtta atatatattgc ttctcctttc      240
tgcaatcgac gtctgacagc tgatttttgc tgttttgnca acntgacgtt tcaccttntg      300
tttcaccant tctggaggaa ttgttnaaca ncttacaaca ctgccttgaa naaannnnan      360
gcctcaaaag ntcttgnnct atnctnnttc ntnnnt
```

<210> 29

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 29

```
gacttgctca tttagagttt gcaggaggct ccatactagg ttcagtctga aagaaatctc      60
ctaagtgtgc tatagagagg gaggtaacag aaagactcct ttagggcatt tttctgactc      120
atgaaaagag cacagaaaag gatgtttggc aatttgctct ttaagtctta accttgctaa      180
tgtgaatact gggaaagtga tttttttctc actcgttttt gttgctccat tgtaaagggc      240
ggagggtcagt cttagtgagg ttgagagttg cttttggcat ttaaatactc taagagaatt      300
aactgtattt cctgtcacct attcactant gcangaaata tacttgctcc aaataagtca      360
ntatgagaag tcaactgtcaa tgaaanttgn tttggt
```

<210> 30

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 30

```
tttttttttt tttttttttg aaatttanaa acaaatttta ttttaagatct gaaatacaat      60
tcctaaaata tcaacttttc canaaaaccg tggctacaca ataagtgcatt gcctctatca      120
tggtanaacg tgcattanac tcaaatacaa aaaccatgaa acaaatcacc atccttcaac      180
aatttgagca aagatagaat gcctaagaac aacatagatg gacttgacaga ggatgggctg      240
ttttacttca agcnccataa aaaaaaaaaa gagcncaaat gcattgggtt ttcaggnta      300
tacattaagn ngaacctttg gcactaggaa tcagggcggt ttgtcacata gcnttaacac      360
atnttaaaaa attntgtant gtcaaagga tangaa
```

<210> 31

<211> 396

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 31
 gacggggccag ggccatctgg aaaggggaact cggtttttcc agaacgtggt ggatcatctg 60
 tcgggtgtgt ggtgaacacg ttcagttcat cagggcctac gctccgggaa gggggcccca 120
 gctgtggctc tgccatgccg ggctgtgttt gcagctgtcc gagtctccat ccgccttttag 180
 aaaaccagcc acttcttttc ataagcactg acagggccca gccacagcc acaggtgcga 240
 tcagtgcctc acgcaggcaa atgcactgaa acccaggggc acacnncgc agagtgaaca 300
 gtgagttccc ccgacagccc acgacagcca ggactgcctt cccaccccn ccccgacccc 360
 angancacgg cacacanntc ancctctnan ctngct 396

<210> 32
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 32
 cgactggcct catacctgt ctacacagtc cctgcacagg gttcctaacc tgtggttagt 60
 aaagaatgtc actttctaac aggtctggaa gctccgagtt tatcttgga actcaagagg 120
 agaggatcac ccagttcaca ggtatttgag gatacaaacc cattgctggg ctgggcttta 180
 aaagtcttat ctgaaattcc ttgtgaaaca gagtttcac aaagccaatc caaaaggcct 240
 atgtaaaaat aaccattctt gctgcacttt atgcaaataa tcaggccaaa tataagacta 300
 cagtttattt acaatttggt tttacaaaa atgaggacta nagagaaaaa tgggtgtcca 360
 aagcttatca tacatttgtc attaagtcct agtctc 396

<210> 33
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 33
 cctttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 120
 nngnnntntn nnnnannaaa aaaaaaaaaa aannnnnnna aaaaaaannn nnnnnnnnnt 180
 tttnnngggg gnttttnann gnantttnn nttnnnnnaa anccccnnng ggnngggggg 240
 nntnnnnnng gnaaaaaaan nnnnnggggn cnnnngggnc cncnccnann nnnnaaaann 300
 nnnggntttt tntnttttna aaaaaanngn nnnnnaacaa aanttttttn nnaanttttn 360
 gggggaaaann nccntttnt ttttttnnan nnnnnn 396

<210> 34
 <211> 396
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 34

acggaccnag	ctggaggagc	tgggtgtggg	gtgcgttggg	ctggtgggga	ggcctagttn	60
gggtgcaagt	angtctgatt	gagcttgtgt	tgtgctgaag	ggacagccct	gggtctaggg	120
ganagagncc	ctgagtgtga	gacccacctt	ccccngtccc	agccctctcc	anttccccca	180
gggacggcca	cttcctgntc	cccgacncaa	ccatggctga	agaacaaccg	caggtcgaat	240
tgttctntgaa	ggctggcagt	gatggggcca	agattgggaa	ctgcccattc	tcccacagac	300
tgttnatggt	actgtggctc	aaggnagtca	ccttcaatgt	taccaccnnt	gacacaaaaa	360
ggcggaccna	nacagtgcna	aagctgtgcc	canngg			396

<210> 35

<211> 396

<212> DNA

<213> Homo sapien

<400> 35

tcgacaaaaa	tcaaatctgg	cactcacaag	ccctggccga	ccccaatgg	gttttaccac	60
tccccctcta	gacctgtct	tgcaaatcc	tctccctagc	cagctagtat	tttctgggct	120
aaagactgta	caaccagttc	ctccatttta	tagaagttta	ctcactccag	gggaaatggt	180
gagtcctcca	acctcccttt	caaccagtcc	catcattcca	accagtggta	ccatagagca	240
gcaccccccg	ccaccctctg	agccagtagt	gccagcagtg	atgatggcca	cccatgagcc	300
cagtgtctgac	ctggcaccca	agaaaaagcc	caggaagtca	agcatgcctg	tgaagattga	360
gaaggaaatt	attgataaccg	ccgatgagtt	tgatga			396

<210> 36

<211> 396

<212> DNA

<213> Homo sapien

<400> 36

tcgacgggaa	gagcctgcta	cggtggactg	tgagactcag	tgactgtcc	tcctcccagc	60
gacccccacg	tggacccct	gccggaccct	ccacccttcg	gcccccaagc	ttcccagggg	120
cttccttttg	actggactgt	ccctgtcat	ccattctcct	gccacccccca	gacctcctca	180
gctccagggt	gccacctcct	ctcgccagag	tgatgaggtc	ccggcttctg	ctctccgtgg	240
cccatctgcc	cacaattcgg	gagaccacgg	aggagatgct	gcttgggggt	cctggacagg	300
agccccacc	ctctcctagc	ctggatgact	acgtgaggtc	tatatctcga	ctggcacagc	360
ccacctctgt	gctggacaag	gccacggccc	agggcc			396

<210> 37

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 37

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cgacgggtgtc agcaactggc catgccacag cacataaaga ttacagtgc aagaaaaaca      60
ttgtttgagg attcctttca acagataatg agcttcagtc cccaagatct gcgaagacgt      120
ttgtgggtga tttttccagg agaagaaggt ttagattatg gaggtgtagc aagagaatgg      180
ttctttcttt tgtcacatga agtggtgaac ccaatgtatt gcctgtttga atatgcaggg      240
aaggataact actgcttgca gataaacccc gcttcttaca tcaatccaga tcacctgaaa      300
tattttcgtt ttattggcag atttattgcc atggctctgt tccatgggaa aattcataga      360
cacgggtttt tcttttccat tctataagcg tatctt      396

```

```

<210> 38
<211> 396
<212> DNA
<213> Homo sapien

```

```

<400> 38
cgacccaaat gataaatagc tttagaatg tgctaattgat aaatgattac atgtcaattt      60
aatgtactta atgtttaata ctttatttga ataattacct gaagaatata ttttttagta      120
ctgcatttca ttgattctaa gttgcacttt ttacccccat actgttaaca tatctgaaat      180
cagaatgtgt cttacaatca gtgatcgttt aacattgtga caaagtttaa tggacagttt      240
tttcccatat gtatatataa aataatgtgt ttacaatca gtggcttaga ttcagtgaaa      300
tacagtaatt cattcaatta tgatagtatc tttacagaca ttttaaaaat aagttatttt      360
tatatgctaa tattctatgt tcaagtggaa tttgga      396

```

```

<210> 39
<211> 396
<212> DNA
<213> Homo sapien

```

```

<400> 39
tcgaccaaga atagatgctg actgtactcc tcccaggcgc cccttcccc tccaatccca      60
ccaaccctca gagccacccc taaagagata ctttgatatt ttcaacgcag ccctgctttg      120
ggctgccctg gtgctgccac acttcaggct cttctccttt cacaaccttc tgtggctcac      180
agaacccttg gagccaatgg agactgtctc aagagggcac tgggtggccc acagcctggc      240
acagggcaag tgggacaggg catggccagg tggccactcc agacccttg cttttcactg      300
ctggctgcct tagaaccttt cttacattag cagtttgctt tgtatgcact ttgttttttt      360
ctttgggtct tgtttttttt ttccacttag aaattg      396

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<210> 40
<211> 396
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

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<400> 40
tttttttttt ttttgttatt tagtttttat ttcataatca taaacttaac tctgcaatcc      60
agctaggcat gggagggaac aaggaaaaa tggaacccaa agggaaactgc agcgagagca      120
caaagattct aggatactgc gagcaaatgg ggtggagggg tgctctcctg agctacagaa      180
ggaatgatct ggtgggtaan ataaaacaca agtcaaactt attcgagttg tccacagtca      240
gcaatgggtga tcttcttgct ggtcttgcca ttcctggacc caaagcgctc catggcctcc      300
acaatattca tgccttcttt cactttgcca aacaccacat gcttgccatc caaccactca      360
gtcttggcag tgcanatgaa aaactgggaa ccattt      396

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<210> 41
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 41
 tcgacctctt gtgtagtcac ttctgattct gacaatcaat caatcaatgg cctagagcac 60
 tgactgttaa cacaaacgtc actagcaaag tagcaacagc tttaagtcta aatacaaagc 120
 tgttctgtgt gagaattttt taaaaggcta cttgtataat aacccttgtc atttttaatg 180
 tacaaaacgc tattaagtgg cttagaattt gaacatttgt ggtctttatt tactttgctt 240
 cgtgtgtggg caaagcaaca tcttccttaa atatataatta cccaaagnaa aagcaagaag 300
 ccagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat 360
 ggtgagaggc aaggcatgag agggcaagtt tgttgt 396

<210> 42
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 42
 cttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
 aaaanccnna nnaananang gnaannnann aaaaaannca aaccncntnt anaaaangcc 120
 nntntnaggg ggggggttca aaaccaaang gnngntngga ngnaaannna aaanttnnnn 180
 gggggnanaa anaaaaaggg nngaaanntg acccnanaan gaccngaaan cccgggaaac 240
 cnngggntan aaaaaaagnt gancctctaa nnccccgna aaanggggga agggnaannc 300
 caaatccnnt gnggggttggg gngggggaaa aaaaaaaccc cnaaaaantg naaaaaaccg 360
 ggnttnaaan atttgggttc gggggntttn tnttaa 396

<210> 43
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 43
 tttttttttt ttttgcttca ctgctttatt ttgaaatca caagcaattc aaagtgatca 60
 tcattgaggc ttctgttaaa agttcttcca aagttgcccga gttttaanat taaacaatat 120
 tgcactttta gatgaactaa cttttgggat tctcttcaaa gaaggaaagt attgctccat 180
 ctgtgctttt cttanactaa aagcactactg canaaaactc tattttaaaa atcaaacactg 240
 cagggtacag taacatagta aagtacctgc ctattttana atcctanaga acatttcatt 300
 gtaagaaact agcccattat ttaagtgtcc acagtatttt tcatttcant ggtccaagat 360

gccaaaggttt ccaaacacaa tcttggtctc taatac 396

<210> 44
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 44
 gacctagttt tacctcttaa atatctctgt tcccttctaa gttggttgct gtgttttctt 60
 cagagcaaga aggttatatt ttttaaaatt tacttagtaa tgcacattca aaacacacat 120
 caagtcttca ggataaagtt caaaaccgct gtcattggccc catgtgatct ctccctcccc 180
 taccctctca tcatcttagtt tcttctgcgc aagccactct ggcttccttt cagttttgtg 240
 gttcccggtt ttagctagtt cagtgggttt caatgggcat ttcttgccct tttttttcta 300
 aacgacaaat agaaatacat cttctttatt atcctccaaa tccaattcag aggtaatatg 360
 ctccacctac acacaatttt agaaataaat taaaaa 396

<210> 45
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 45
 tttttttttt ttttaaannt tntaaatttt taatgaaann ganttagaac aatgtattat 60
 tnacatgtaa ataaaaaaag agancataa ccccatatnc tcnnnaaagg aaggganacn 120
 gcnggccntt tatnagaana nnnnnccatat aagaccccat taagaagaat ctggatctaa 180
 anacttncaa acaggagtct acagtangtg aacagcannc cctaattcca ctgatgtgat 240
 gnttcanaata aaatcancan cgntgatcgg gnacnncanc aatntgancg gaanannact 300
 gctcnatatn ttnnaggann cngatgtggg cattttttac aaagataatg gccacacct 360
 tccngnccga atcgancnga nctcccnntt ctgtgn 396

<210> 46
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 46
 tttttttttt tttttttttc tganacagag tctcattctg ttgcctaggc tggattgcag 60
 tgggtgccatc tcggctcact gcaacctccg cctcctgggt tccanaaatt ctcttgctc 120
 agcctcccgg gtagctggga ctanaggcac acgccaccac gccaggctaa tttttatatt 180
 tttagtanan atggcgtttc accatgttga ccanactgat ctcgaaactcc cgacctcgtg 240
 atccaccacac ctcgccctcc caaagtgtg ggattacagg cgtgaaacca ccaggcccgg 300
 cctgaaatat ctatttnttt tcagattatt tttaaaattc catttgatga atcttttaaa 360
 gtgagctana naaagtgngt gtgtacatgc acacac 396

<210> 47

<211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 47
 tttttttttt ttttttttgc tttgccaact gtttattcag ggccctgaac ggggtgggtgcg 60
 tggacatgca acacactcgg gccacacagca gcgtgaccgg ccgctcccaa gccccgggcg 120
 cacaaccaca gccaggagca gcccttgcca ccaactgggc accgtccagg gccccacagg 180
 accagccgaa ggtgccccgg gccgaggcca gctgggtcag gtgtaccctc agcctgggggt 240
 tgagtgagga gcggcaccac cagtatcctg tgtaccccaa gttgcccaagn aggccgaggg 300
 ggcccttgggc tccatctgca ctggccaccc cgtgccaaagc atcacagctg cgtgagcagg 360
 tttgtgtgtg agcgtgtggc ggggcctggt tgtccc 396

<210> 48
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 48
 ctgggcctgt gccgaagggt ctgggcagat cttccaaaga tgtacaaaat gtagaaattg 60
 ccctcaagca aatgcaaaga tgctcaacac ccttagtcat caagaaaatg caaatggaat 120
 ccacagagag atactgcaca ctgacaaaga tggctgtatt actaaagggt aataaccagc 180
 gcggggggca cgtggagtca ctggaacatt tgtgcaatgc tgggtgggaat gtcaaccctg 240
 gcggccctct ggaataagcc tggcagctcc tccaagagtt acccgtgtga ccagcaatt 300
 ccactcctag ctccaccac aggaattgaa agcaaagacg caaacagatg cctgtgcacc 360
 aaagttcacg gcagcatcct tcgccatagt ggnaaa 396

<210> 49
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 49
 accccaaaat gggaaaggaa aagactcata tnaacattgn cgtnattgga cacgtacatt 60
 cggncaaagn caccactact ggnatntga tntataaatg cggnggcac gacanaanaa 120
 ccatngnaan atttganaag gaggtgctg atatnggaaa gggctcctc nantntgcct 180
 gggctcttga tnaactgaaa nctgancntg aacgtgggnt caccattgat atctncttgt 240
 ggaaatntna gaccancann tactatgtna ctatcattga tgccccagga cacaganact 300
 ttatcnaaan catgattacn nggacatnta nagctgactg tgctngcctg attgtngctg 360
 ctggtgttgg tgaatttgaa nctggtatnt ccaana 396

<210> 50
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 50
 cgacttcttg ctggtgggtg gggcagtttg gtttagtggt atactttggt ctaagtattt 60
 gagttaaaact gcttttttgc taatgagtgg gctggttggt agcagggttg tttttcctgc 120
 tggtgattgt tactagtggc attaactttt agaatttggg ctggtgagat taattttttt 180
 taatatccca gctagagata tggcctttaa ctgacctaaa gaggtgtggt gtgatttaat 240
 tttttcccg tcttttttct tcagtaaacc caacaatagt ctaaccttaa aaattgagtt 300
 gatgtcctta taggtcacta cccctaaata aacctgaagc aggtgttttc tcttgacat 360
 actaaaaaat acctaaaagg aagcttagat gggctg 396

<210> 51
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 51
 tttttttttt ttcagcgngg atttatttta tttcattttt tactctcaag anaaagaana 60
 gttactattg caggaacaga cattttttta aaaagcgaaa ctcttgacac ccttaaaaca 120
 gaaaacattg ttattcacat aataatgngg ggctctgtct ctgccgacag gggctgggtt 180
 cgggcattag ctgtgccgtc gacaatagcc ccattcacc cttcataaa tgctgctgct 240
 acaggaaggg aacagcggct ctccanaga gggatccacc ctggaacacg agtcacctcc 300
 aaagagctgc gactgtttga naatctgcc aaggaaaac cactcaatgg gacctggata 360
 acccagggcc gggagtcata gcaggatgtg gtactt 396

<210> 52
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 52
 acctcgctaa gtgttcgcta cgcggggcta ccggtcgggt cggaatggc agaggtggag 60
 gagacactga agcgactgca nagccagaag ggagtgcagg gaatcatcgt cgtgaacaca 120
 gaaggcattc ccatcaagag caccatggac aacccacca ccaccagta tgccagctc 180
 atgcacagnt tcacctgaa ggcacggagc accgtgcgtg acatcgacc ccagaacgat 240
 ctacacctcc ttcgaattcg ctccaagaaa aatgaaatta tggtgcacc agataaagac 300
 tatttctga ttgtgattca gaatccaacc gaataagcca ctctcttggc tccctgtgtc 360
 attccttaat ttaatgcccc ccaagaatgt taatgt 396

<210> 53
 <211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 53

tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	120
tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	180
tttttttttt	tttttttttt	tttttttttt	tttttttttt	ttannttntt	ttttnttttn	240
cctttntttt	aattcanaaa	aagaanaaga	aaanataana	nnnancnnan	nnnnnnnatn	300
ntncttnata	ntnnttnnnn	nanngggnnn	gcgagnnnnn	nnnnnnnnnn	nttctnnnnt	360
tnnnnnnctt	gcnccecttn	ntttngnnnn	angcaa			396

<210> 54

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 54

ctcttggggc	tgctgggact	cgcgtcggtt	ggcgactccc	ggacgtaggt	agtttggttg	60
gccgggttct	gaggcettgc	ttctctttac	ttttccactc	taggccacga	tgccgcagta	120
ccagacctgg	gaggagtcca	gccgcgctgc	cgagaagctt	tacctcgctg	accctatgaa	180
ggcacgtgtg	gttctcaaat	ataggcatte	tgatgggaac	ttgtgtgtta	aagtaacaga	240
tgatttagtt	tgtttggtgt	ataaaacaga	ccaagctcaa	gatgtaaaga	agattgagaa	300
attccacagt	caactaatgc	gacttatggt	agccaaggaa	gcccgcaatg	ttaccatgga	360
aactgantga	atggtttgaa	atgaagactt	tgctgt			396

<210> 55

<211> 396

<212> DNA

<213> Homo sapien

<400> 55

cgacggtttg	ccgccagaac	acagggtgtc	tgaaaactac	ccctaaaagc	caaaatggga	60
aaggaaaaga	ctcatatcaa	cattgtcgtc	attggacacg	tagattcggg	caagtccacc	120
actactggcc	atctgatcta	taaatgcggt	ggcatcgaca	aaagaaccat	tgaaaaattd	180
gagaaggagg	ctgctgagat	gggaaagggc	tccttcaagt	atgcctgggt	cttggataaa	240
ctgaaagctg	agcgtgaacg	tggtatcacc	attgatatct	ccttgtggaa	atttgagacc	300
agcaagtact	atgtgactat	cattgatgcc	ccaggacaca	gagactttat	caaaaacatg	360
attacaggga	catctcaggc	tgactgtgct	gtcctg			396

<210> 56

<211> 396

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 56
 tttttttttt tttttttctca ttttaactttt ttaatgggtc tcaaaattct gtgacaaatt 60
 tttgggtcaag ttgtttccat taaaaagtac tgatttttaa aactaataac ttaaaactgc 120
 cacacgcaaa aaanaaaacc aaagnggtcc acaaaacatt ctcttttcct tctgaagggt 180
 ttacgatgca ttgttatcat taaccagtct tttactacta aacttaaattg gccaatgaa 240
 acaaacagtt ctganaccgt tcttccacca ctgattaana gtgggggtggc aggtattagg 300
 gataatattc atttagcctt ctgagctttc tgggcanact tggngacctt gccagctcca 360
 gcagccttnt tgtccactgc tttgatgaca cccacc 396

<210> 57
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 57
 cctttttttt tttttttttt tttttttttt tttttttttt tttttttttt tnaaaanntt 60
 ntttttgcaa anccnancaa aaanggnngg aangaaaaan nggaaaaatt ntttttncnt 120
 ntttggaac nnnnagccct tnntttgaaa aaangnggnc ttaaaanngn tgaannaaag 180
 gnnanncccn gntncttnnn tttaaaaana anggggnngn ttttttttaa anaanatttt 240
 ttttttcctt aanancnnn anntgaaacn ngncnccn nctnncttna aagggnnnaa 300
 atnanangnn aaaaaanccc tnancceccc ccttanntt tncnannana naaagnctt 360
 ttgggncttg naaaaaanaa cctttttntt gcnttn 396

<210> 58
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 58
 cgacctcaaa tatgccttat tttgcacaaa agactgcaa ggacatgacc agcagctggc 60
 tacagcctcg atttatat ttgtttgtgg tgaactgatt ttttttaaac caaagttag 120
 aaagaggttt ttgaaatgcc tatggtttct ttgaatggta aacttgagca tcttttcact 180
 ttccagtagt cagcaaagag cagtttgaat tttcttgcg ctccctatca aaatattcag 240
 agactcgagc acagcaccca gacttcatgc gcccggtggaa tgctcaccac atgttggtcg 300
 aagcggccga ccaactgactt tgtgacttag gcggctgtgt tgcctatgta gagaacacgc 360
 ttcaccccca ctccccgtac agtgcgcaca ggcttt 396

<210> 59
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)

<223> n = A,T,C or G

<400> 59

cttttttttt	tttttttttt	tcagnggaaa	ataactttta	ttganacccc	accaactgca	60
aaatctgttc	ctggcattaa	gtccttctt	cctttgcaat	tcgggtcttc	ttcagnggtc	120
ccatgaatgc	tttcttctcc	tccatggtct	ggaagcggcc	atggccaaac	ttggaggngg	180
tgtcaatgaa	cttaaggnca	atcttctcca	nagcccgccg	cttcttctgc	accancaagg	240
acttgcggag	ggngagcacc	cgttnttgg	ttcccaccac	ncagccttc	agcatgacaa	300
agtcattggt	cacttcacca	tagnggacaa	agccacccaa	agggttgatg	ctccttgga	360
aataggncat	agtcacngga	ggcattgtnc	ttgatc			396

<210> 60

<211> 396

<212> DNA

<213> Homo sapien

<400> 60

acctcagctc	tcggcgcacg	gcccagcttc	cttcaaaatg	tctactgttc	acgaaatcct	60
gtgcaagctc	agcttggagg	gtgatcactc	tacaccccca	agtgcataatg	ggtctgtcaa	120
agcctatact	aactttgatg	ctgagcggga	tgctttgaac	attgaaacag	ccatcaagac	180
caaaggtgtg	gatgaggtca	ccattgtcaa	cattttgacc	aaccgcagca	atgcacagag	240
acaggatatt	gccttcgcct	accagagaag	gacaaaaaag	gaacttgcac	cagcactgaa	300
gtcagcctta	tctggccacc	tggagacggt	gattttgggc	ctattgaaga	cacctgctca	360
gtatgacgct	tctgagctaa	aagcttccat	gaaggg			396

<210> 61

<211> 396

<212> DNA

<213> Homo sapien

<400> 61

tagcttgtcg	gggacggtaa	ccgggacccg	gtgtctgtct	ctgtcgcttc	cgctctctaa	60
tcctagcca	ctatgcgtga	gtgcatctcc	atccacgttg	gccaggctgg	tgtccagatt	120
ggcaatgcct	gctgggagct	ctactgcctg	gaacacggca	tcagcccgga	tggccagatg	180
ccaagtgaca	agaccattgg	gggaggagat	gactccttca	acaccttctt	cagtgcagacg	240
ggcgctggca	agcacgtgcc	ccgggctgtg	tttgtagact	tggaaaccac	agtcattgat	300
gaagttcgca	ctggcaccta	ccgccagctc	ttccaccctg	agcagctcat	cacaggcaag	360
gaagatgtcg	ccaataacta	tgcccagagg	cactac			396

<210> 62

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 62

tcgacgtttc	ctaaagaaaa	ccactctttg	atcatggctc	tctctgccag	aattgtgtgc	60
actctgtaac	atctttgtgg	tagtcctgtt	ttcctaataa	ctttgttact	gtgctgtgaa	120
agattacaga	tttgaacatg	tagtgtacgt	gctgttgagt	tgtgaactgg	tgggccgtat	180
gtaacagctg	accaacgtga	agatactggt	acttgatagc	ctcttaagga	aaatttgctt	240
ccaaatttta	agctggaaag	ncactggant	aactttaaaa	aagaattaca	atacatggct	300

```

ttttagaatt tcnttacgta tgттаagatt tnggtacaaa ttgaantgtc tgnctganc      360
ctcaaccaat aaaatctcag tttatgaaan aaannn                                396

```

```

<210> 63
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1) ... (396)
<223> n = A,T,C or G

```

```

<400> 63
ttnttttttt nttttntntt ttntcnttgn ttgnacngaa cccggcgctn ntccccacn      60
nnnnacggcc gcccntattc annntntcnt canntannna ccgcaccctc ggactgcnnn      120
tngggccccc ccgncnannc nccnncccc anttncgcgc cgcgcgcgcc gccttttttt      180
attggcnncc atnanaaccg gggnacacct ncangngcgc cnaaantngg ggcangactc      240
anagggggcc atcaaccncc aagnncaanc tgganctcta caaacggcct acgntttntg      300
nccatgnggg tagggnttta cccgcnatga tgannatgnn aanaactttn ncaanccctt      360
tattaaccaa tngngtgngg agacgggaacn tggtta                                396

```

```

<210> 64
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1) ... (396)
<223> n = A,T,C or G

```

```

<400> 64
tcgacgtcgg ggttttctgc ttcaacagtг cttggacgga acccggcgct cgttccccac      60
cccgcccgcc cgcctatagc cagccctccg tcacctcttc accgcaccct cggactgccc      120
caaggccccc gccgcgcgtc cagcgcgcgc cagccaccgc cgcgcgcgcc gcctntnctt      180
agtgcgcgcc atgacgaccg cgtccacctc gcaggtgcgc cagaactacc accaggactc      240
agaggccgcc atcaaccgcc agatcaacct ggagctctac gcctcctacg tttacctgtc      300
catgtcttac tactttgacc gcgatgatgt ggctttgaan aactttgcca aatactttct      360
tccaatctc atgaggagaa ggaacatgct ganaaa                                396

```

```

<210> 65
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1) ... (396)
<223> n = A,T,C or G

```

```

<400> 65
tttttttttt tttttttttt ttttnacca ataatgcttt tattttccac atcaanatta      60
atztatatgt tagttttagt acaagtacta aaatgtatac ttnttgccct aatagctaag      120
gnatacataa gcttcaccat acatnttgca nccnctgtc tgcctatgt cattgttata      180

```

aatgtanana	ttttaggaaa	ctnttttatt	caacctggga	catntatact	gtaggagtta	240
gcactgacct	gatgtnttat	ttaaaagtaa	tgnatattac	ctttacatat	attccttata	300
tattnaaacg	tatttccatg	ttatccagct	taaaatcaca	tggnnggttaa	aagcatgagt	360
tctgagtcaa	atctggactg	aaatcctgat	gctccc			396

<210> 66
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 66						
tcgacttttt	tttttccagg	acattgtcat	aattttttat	tatgtatcaa	attgtcttca	60
atataagtta	caacttgatt	aaagttgata	gacatttgta	tctattttaa	gacaaaaaaa	120
ttcttttatg	tacaatatct	tgtctagagt	ctagcaaata	tagtaccttt	cattgcagga	180
tttctgctta	atataacaag	caaaaacaaa	caactgaaaa	aatataaacc	aaagcaaacc	240
aaaccccccg	ctcaactaca	aatgtcaata	ttgaatgaag	cattaaaaga	caaacataaa	300
gtaacttcag	cttttatcta	gcaatgcaga	atgaatacta	aaattagtgg	caaaaaaaca	360
aacaacaaac	aacaaacaaa	acaaaacaaa	caaaca			396

<210> 67
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 67						
acgcttttgt	ccttcatttt	aactgttatg	tcatactgtt	atgttgacat	atctctttat	60
aagagaatag	aggcaaaagt	atagaactga	ggatcatttg	tatttttgag	ttggaaatta	120
tgaaacttca	ccatattatg	atcatacata	ttttgaagaa	cagactgacc	aaagctcacc	180
tgttttttgt	gttaggtgct	ttggctgaac	ttgattccag	cccccttttc	cctttggtgt	240
tgtgtatgtc	gtttcatttc	ctctcaaadc	ttcaactctt	gccccatgtc	tccttggcag	300
caggatgctg	gcatctgtgt	agtcctcata	ctgtttactg	ataaccacaa	aattcatttt	360
catggcagac	ctaagctcag	accctgcctt	gtcctg			396

<210> 68
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 68						
acctgagtc	tgctctttct	ctctccccgg	acagcatgag	cttcaccact	cgctccacct	60
tctccaccaa	ctaccggtcc	ctgggctctg	tccaggcgcc	cagctacggc	gcccggccgg	120
tcagcagcgc	ggccagcgtc	tatgcaggcg	ctgggggctc	tggttcccgg	atctccgtgt	180
cccgtccac	cagcttcagg	ggcggcatgg	ggtcgggggg	cctggccacc	gggatagccg	240
ggggtctggc	aggaatggga	ggcatccaga	acgagaagga	gaccatgcaa	agcctgaacg	300
accgcctggc	ctcttacctg	gacagagtga	ggagcctgga	gaccgagaac	cggaggctgg	360
agagcaaaat	ccgggagcac	ttggagaaga	agggac			396

<210> 69
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)

<223> n = A,T,C or G

<400> 69

```
ntcncngnng ntgtggtntt ttttttaatt tttatntttt cttttttttt ctngctagen      60
cttncttttt ttggaattnc ggtncctttt tntntcnatt ttttngacaa aaanaacctn      120
ttnttttnana ccanagnnng gnnacnctt nnaatntncc ctttttncgn tngggagctn      180
cncnttnnnc gccnactca ntegagacng tctttttnnn tnnancannn tngtncggt      240
gnengcnttn ntncannant ntccctatn naentgnnt cncncatnt tggacnancn      300
cctagccttn ccatntttt nttnttttn natnancctn gaaaacntcn gntntttcnc      360
nnctttnccn cncncnctt cntatgtncn atgnnc
```

<210> 70

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 70

```
tttttttttt tttntttttt tttttttttt tttttttntt tttttttttt tttttntnc      60
aannntnaa cttttaanng gccncngcn cccaanggg gacctgctt ttgnnggcta      120
aatgccnaa aactttgggg nantnggtat naaaccnc tttgccnnc annttncngg      180
gggggggggg ttttgnngg ggaacangna naacntttt ncnanggnat caccaaaaan      240
aaagcccnnc cttttttccn annggggggg ggngggggga aantcanccc ccanattgac      300
cttnatttca aaanggggct tataatcctg ggcntggann cttccctnta cccgggggtt      360
gnccacnttt tattanaggg gnangnggat ccccnt
```

<210> 71

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 71

```
gcacttagag ggcngttaa ntctagagg cngnntaaa cnnnnncatc nacctncnt      60
genectgctn gttgccnccc ntctgtgnet tgcnnnnccc nngagcgtnc cttnaccnnn      120
gaangtgcct nnnnnactga nnnnnncnna taanatnggg anantncgtc gncattntnt      180
natnnggggt gatgtattc tgggggggtg ggngggngna tnnnatactn nggggacgtn      240
nnatnangag nnatntcnng nttntctnt gnttttnggg gggcnatng nnntctntnn      300
ggactntcg cncannnate aatancttna ttcngtgtan ngtccegnccn tagnnnngcn      360
ngtactnnan ngttgnntc attactnttc gtngg
```

<210> 72

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 72
 tntttttttt tttctaaaac atnactnttt attnnnnang nttnttgaac ctctnngcnt 60
 natggtgaga gtttgtctga ttaataanaa tngganntt nannanangc ntgnncgcaa 120
 ngatggcnnc nctgtatac ccaccatccc attacactnt gaaccttttn tttgattaat 180
 aaaaggaagg natgcgggga anggggaaag agaattgcttg aacattncca tgnngccttn 240
 gacaaacttt ccaatggagg cnggaacnaa nnaccaccan ncaactcccc tttttgtaat 300
 ttnnnaactt ncaacnncta nctntttatt ttggntcccc tggnggaaac agnctgtatn 360
 annnnnaagn ccentgagaac atccctggnt nncnna 396

<210> 73
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 73
 ntcaacntng actnctgtga ggnatggtgc tggngngcnta tgcngtgngn ttttggatac 60
 naccttatgg acantngcnn tcccnnggaa ngatnataat ncttactgna gnnactnnaa 120
 nnttcctnt cnaaaangtt naaaancatt ggatgtgcc caatgatgac agtttatttg 180
 ctactcttga gtgctataat gatgaagatc ttanccacca ttatcttaac tgangcacc 240
 aanatggtga nttggggaac atatanagta caactaagtt cacatgaagt tgtttnttcc 300
 caggnnctaa agagcaagcc taactcaagc cattgncaca caggtgagac acctctattt 360
 tgtactctc acttttaagg gattagaaaa tagcca 396

<210> 74
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 74
 cctttttttt tttttttact gngaatatat actttttatt tagtcatttt tgtttacaat 60
 tgaaactctg ggaattcaaa attaacatcc ttgcccgtga gcttcttata gacaccanaa 120
 aaagtttcaa ccttgtgttc cacattgttc tgctgtgctt tgtccaaatg aacctttatg 180
 agccggctgc catctagttt gacgcggatt ctcttgccca caatttcgct tgggaagacc 240
 aagtcctcaa ggatggcatc gtgcacagct gtcagagtac ggctcctggg acgcttttgc 300
 ttattttttg tacggctttt tcgagttggc ttaggcagaa ttctcctctg agcgataaag 360
 acgacatgct tcccactgaa ctttttctcc aattcg 396

<210> 75
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 75
 tttttttttt tttntttttt tttttttttt ttttttttaa ntntaanggg gangggccct 60
 ttttttttaa ctngnccntt ttnttttctt ttttttaaaa ggaaaaaaa anntttnttt 120
 ttntttttaa aacccttttt cccacnaaca aaaaaaacn ttcccntnc cttttnnna 180
 aaaaaagg gctnggnntt tcccttann caaaaaacn tntccnngg naaaaaant 240
 ntnccgggg gggaacnnn tgggggtgt nccnaattt gggggcctc ggaaggggg 300
 nncncncct aaangtnt ttcaaaaaa aaaccccnt cctntntaa aaaaaana 360
 aanaangnn ngntttttt ntnttnnc cccaa 396

<210> 76
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 76
 acattcttca gaaatacagt gatgaaaatt cattttgaaa ctcaaattt ttcatcttgg 60
 atattctcct gtttttatta aaccagnat tacnctggc cntccctnta atgttctag 120
 gaaggcatgt ctgttgnnt tnnnnnaaaa nnaattntt ttttttngn naaacccaa 180
 atcccantt atcaggaagt tagncnaatg aaatggaaat tggntaatg acaaaagcta 240
 gcttgtaaaa aggaccacc nncacnngn ctttaccctc ttggttngt gggggaaaa 300
 ccatnttaa centntggnn aaaattgggn ncntaaagt tncntggna acagtnctn 360
 cngtattnaa ttgncnttat nggaaaatcn gggatt 396

<210> 77
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 77
 tttttttttt tttttttttt tttttttttt tatcaacatt tatatgcttt attgaaagt 60
 ganaanggca acagttaa atnngggacnc cttacaattg tgtaaaaaac atgcncanaa 120
 acatatgcat ataactacta tacaggngat ntgcaaaaac ccctactggg aaatccattt 180
 cattagtta aactgagcat ttttcaaagt attcaaccag ctcaattgaa anacttcagt 240
 gaacaaggat ttacttcagc gtattcagca gctanatttc aaattacnca aagngagtaa 300
 ctnggccaaa ttcttaaaat ttntttaggg gnggtttttg gcatgtacca gtttttatgt 360
 aaatctatnt ataaaagtcc acacctcctc anacag 396

<210> 78
 <211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 78

agctggcnaa	aggngnatgn	gctgcnangc	gattangnnn	ggtaacgtca	nnggntnncc	60
agtgcangac	nttgtaaaac	gacggccaca	tgaattgtaa	tacgactcac	tatngggcgn	120
attgggcegt	gnaggatngt	gntcacactc	gaatgtatnc	tggengatnc	ananngett	180
atngctnttg	acggngnntn	anccanctng	ggctttagg	ggatatccct	cgccccctgt	240
tcnttgattt	gcacgggcnn	ctccganttc	cttcataata	ccngacgctt	cnatccccta	300
gctcngacct	ntcantntnt	tcnntgggtt	ntnnccgntc	acngcttncc	cgnangntat	360
aatctnggct	cctttnggga	tccattantc	tttact			396

<210> 79

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 79

caccaacca	aacctggcgc	cgctggcatc	gtagagtga	cacaacccaa	aaacgatacg	60
ccatctgttc	tgccctggct	gcctcagccc	taccagcact	ggcatgtct	aaaggncatc	120
gtattgagga	agttcctgaa	cttcctttgg	tangttgaag	ataaagctga	aggctacaag	180
aagaccaang	aagntgtttt	gctccttaan	aaacttanac	gcctggaatg	atatcaaaaa	240
ngctatgcct	ctcagcgaat	gagactggn	angcaaatg	agaaaccntc	nccgcatcca	300
gcgnaggggc	cgtgcctctc	tatnntgang	atnntggnan	cnttcaaggc	cttcagaacc	360
tcctngaaa	tnctctnctt	taangaacca	aactgn			396

<210> 80

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 80

tgtacatagg	catcttattc	actgcaccct	gtcacaccca	gcaccccccg	ccccgcacat	60
tatttgaaag	actgggaatt	taatggttag	ggacagtaaa	tctacttctt	tttccaggga	120
cgactgtccc	ctctaaagtt	aaagtcaata	caagaaaact	gtctattttt	agcctaaagt	180
aaaggctgtg	aagaaaattc	attttacatt	gggtagacag	taaaaaaca	gtaaaaatac	240
ttgacatgag	cacctttaga	tccttcctt	catggggctt	tgggcccgag	atgacctttg	300
aggcctgtaa	anggattgna	atctcctata	agctgtatag	tggagggtat	ggnggggtcat	360
ttgagtaagc	cctccaagat	acnttcaata	cctggg			396

<210> 81
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 81
 gcagctgaag ttcagcaggt gctgaatcga ttctcctcgg cccctctcat tccacttcca 60
 acccctccca ttattccagt actacctcag caatttgtgc cccctacaaa tgtagagac 120
 tgtatacgcc ttcgaggtct tccctatgca gccacaattg aggacatcct gcatttcctg 180
 ggggagttcg ccacagatat tcgtactcat ggggttcaca tggttttgaa tcaccagggn 240
 ccgccatcag gagatgcctt tatccagatg aagtctgcgg acagancatt tatggctgca 300
 cagaagtggc ataaaaaaaa catgaaggac agatatgttg aagttttcag tgtcagctga 360
 nganagaaca ttgnngtann nggggggnact ttaaat 396

<210> 82
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 82
 gactcagaaa tgtcagtctc atgaagttca aaagatcgag aatgtttgct atcttggtgg 60
 agcagccgca gccaaagcaag taacttgtaa aatgaggaat gccatcacc ctcgagtgtc 120
 catcccat aacttggggg tagagcacia gcgttcccag gaactactca ccttaccatc 180
 ttggccgttt catttgcttc caccagttct ggaaagagan ggcctagaag ttcaaaaaaa 240
 aagtaggaaa ngtgcttttg gagaaaatca cctgctcctc agaactgggc ttacaanctg 300
 ngaagtacnc tatgtgcac ctaatcctca tatatgacct caagagacnc caataagcat 360
 atttccacca cggaatgacc agtgcttttg gtaana 396

<210> 83
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 83
 tttgatttaa ganatttatt atttttttaa aaaaagcaac ttccagggtt gtcattgtac 60
 aggttttgcc cagtctccta tagcatggta tagtgataac tgatttttta taacaatgac 120
 tcagaggcat tgaagatcca taactatctt ctgaattatc acagaaagaa gaaagttaga 180
 agagtttaaat gttaagtgtg ttaaaaaatca tattctaatt cttttaattt ggttatctga 240
 gtatgataat ataggagagc tcagataaca aggaaaaggc attggggtaa gaacactcct 300
 tcccacagga tggcattaac agactttttc tgcataatgt ttatatagtt gccaaactaat 360

tcaccttttta cncagettna ttttttttta ctnggg

396

<210> 84
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 84
 tttttacagc aatttttttt tattgatgtt taacctgtat acaaccatac ccattttaag 60
 ngtagacagaca aatgaatttt gacaaattca ttcactcatc taatcatcac tataaccatg 120
 atacagattt ttatcactcc aaaagtccat cctgtgctct tttcaagtcc atcctcctca 180
 tctgataccc caagccacca ttgttttgc tcttggaact acagttttgg gnttttagaa 240
 tttcatatat ggtngaataca taccatttgn natgtggggc tgacgncttt cctccaataa 300
 tggatttgag aattatctac attttgcac gatcctgggt tatttatacc aacnangggg 360
 tattatgnaa aatnggacca caatttgng gcanta 396

<210> 85
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 85
 cagtgaccgt gctcctaccc agctctgtc cacagcgccc acctgtctcc gcccctcggc 60
 ccctcgcccc gctttgccta accgccacga tgatgttctc gggcttcaac gcagactacg 120
 aggcgtcatc ctcccgtgc agcagcgct ccccgccgg ggatagcctc tcttactacc 180
 actcaccgc agactccttc tccagcatgg gctcgcctgc aacgcgcagg acttctgcac 240
 ggacctggcc gctccagtgc caacttcatt ccacggcact gcatctcgac canccggact 300
 tgcannggtt ggggaanccg cccttgtttc tccgtggccc atctaanacc aaaccntca 360
 ccttttcgga gnccccnccc ctccgntggg nttact 396

<210> 86
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 86
 ttttnnactg aatgtttaat acatttgnag gaacagaaga aatgcagtan ggattaanat 60
 tttataatta gacattaatg taacagatgn ttcatTTTTc aaagaagntn ccccttntc 120
 cctatctttt tttaatcttc cttanagcaa taantagtaa ttactatatt tgtggacaag 180
 ctgctccact gtgntggaca gtaattatta aatctttatg tttcacatca ttattacctt 240

```

ccanaattct accttcattt ccctgcacag gttcactgga ctggntcaca ancaaattgn      300
actccactca antanaagag cccaaagaaa ttagagtaac gncnancct atgaattana      360
gacccaaaga ttnnaggngn tgattagaaa cataan                                396

```

```

<210> 87
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 87
atggaggcgc tggggaagct gaagcagttc gatgcctacc ccaagacttt ggaggacttc      60
cgggtcaaga cctgcggggg cgccaccgtg accattgtca gtggccttct catgctgcta      120
ctgttcctgt ccgagctgca gtattacctc accacggagg tgcctcctga gctctacgtg      180
gacaagtcgc ggggagataa actgaagatc aacatcgatg tactttttcc ncacatgcct      240
tgtgcctatc tgagtattga tgccatggat gtggccngag aacancagct ggatgnggaa      300
cacaacctgt ttaagccacc actagataaa gatgcatccc ngtgagctca nagctgagcg      360
gcctgagctt gngaaantcn aggtgaccgg gtttga                                396

```

```

<210> 88
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 88
tccagagcag agtcagccag catgaccgag cgccgcgtcc ccttctcgct cctgcggggc      60
cccagctggg accccttcg cgactggtac ccgcatagcc gctcttcgac caggccttcg      120
ggctgccccg gctgcgggag gagtggctgc agtggttagg cggcagcagc tggccaggct      180
acgtgcgccc cctgcccccc gccgcctega gagccccgca gtggccgcgc ccgctacagc      240
cgcgcnctc agccgggaac tcacancggg gctcggagat ccgggacact gcggaccgct      300
ngcgctgcc ctggatgtca ccacttngc ccggacaact gacggtana caaggatggg      360
gggtgganan nccngtaanc caagaanggg naggac                                396

```

```

<210> 89
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 89
gagagaacag taaacatcca gccttagcat ctctcangag tactgcagat cttcattagc      60
tatattcaca tggagnaatg ctattcaacc tatttctctt atcaaaacta attttgtatt      120

```

```

ctttgaccaa tgttcctaaa ttcaactctgc ttctctatct caatcttttt cccctttctc   180
atctttcctc cttttttcag ttcttaactt tcactgggtc tttggaatgn tttttctttc   240
atctcttttc ttttacattt tgggggtgtc cctctctttt cttacctctt ttctncatcc   300
ttcttnttct tttgaattgg ctgcccttta tctctctatc tgetgncatc ttcattttctc   360
ctccctctcn ttctcnntca ttctactctc tccent                                     396

```

```

<210> 90
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 90
gggcgcggcg gcgccecccc acccccgcgc cagctctcgt cgcgcgcgcg tccgctgggg   60
gcggggagcg gtccgggcgg cngcggtcgg ccggcggcag ggtgggtgcg tttcnttttn   120
nattnccnc nttctctctn nttnnnnnnn ctntanncn nttncttcn cnnntttnc   180
tntntctna cennnttttn taatctctt ctntnnnnn tctcttnnat ntnttctta   240
nttctnnnn tttntctnt ctttctctc ctnttctcn nctcnnnc tcnncatctt   300
nntntttnt ncctctntt cttnttctn ntntntttt nnnnttctnt tntcatntt   360
ncctntntta ctntcanctt ntatnnnctt cntttt                                     396

```

```

<210> 91
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 91
ntntcctnna tttttnnntc nctttttttt ttnaattttt cttnttttn tttataaaaa   60
tcnncacnta aaacngcgga anaggggatt tntnttngg gngtanncn nggcncaaa   120
naaccccaaa aatancccaa atgcacagg nccnggnaa angaccnacn tgggtntttt   180
ntttntnaac aaggggggtt ttaaagggn tnggnatcaa aggnataaaa nttaaacct   240
ttganaaaatt ttttaanagg cttgcccccc actttggncc cnccccncn gnngggatcc   300
aatTTTTTTT cnttggggct ccngncccn nanntccgg gttnttggn nntcctnntt   360
tttttttttt tgccttcacc cntnccattn cntttt                                     396

```

```

<210> 92
<211> 396
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

```

```

<400> 92

```

```

ctnttttnnt ntttttttcc ccatcatcca naaatgggtt ttattctcag ccgagggaca      60
gcaggactgg taaaaactgt caggccacac ggttgctgc acagcaccce catgcttggt      120
aggggggtgg agggatggcg ggggctggnt gnccacaggc cgggcatgac aaggaggctc      180
actggagggtg gcacactttg gagtgggatg tcgggggaca ncttctttgg tanttgggcc      240
acaagattcc caaggatanc acnnnnactg attnccannc tanagncaag cggntggcca      300
tntgtangnn nttntntatn tgactattta tagattttta tanaacaggg naagggcata      360
ccncaaaagg gnccaanttt ttaccnccgg gcncce

```

```

<210> 93
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (396)
<223> n = A,T,C or G

```

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<400> 93
gctgccacag atctgttctt ttgtccgttt ttgggatcca caggccctat gtatttgaag      60
ggaaatgtgt atggctcaga tcctttttga aacatatcat acaggttgca gtcctgaccc      120
aagaacagtt ttaatggacc actatgagcc cagttacata aagaaaaagg agtgctaccc      180
atgtttctcat ccttcagaag aatcctgcga acggagcttc agtaatatat cgtggcttca      240
catgtgagga agctacttaa cactagttac tctcacaatg aaggacctgn aatgaaaaat      300
ctgnttctaa ccnagtcctn tttanatttt agngcanatc cagaccancg ncgggtgctcg      360
agtaattctt tcatgggacc tttggaaaac tttcag

```

```

<210> 94
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (396)
<223> n = A,T,C or G

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```

<400> 94
tgccttaacc agtctctcaa gtgatgagac agtgaagtaa aattgagtgc actaaacgaa      60
taagattctg aggaagtctt atcttctgca gtgagtatgg cccaatgctt tctgnngcta      120
aacagatgta atgggaagaa ataaaagcct acgtgttggt aaatccaaca gcaagggaga      180
tttttgaatc ataataactc atanngtgct atctgtcagt gatgccctca gagctcttgc      240
tgntagctgg cagctgacgc ttctangata gttagnntgg aaatggtctt cataataact      300
acacaaggaa agtcancnc cgggcttatg aggaattgga cttaataaat ttagngngct      360
tcnacctaa aatatatctt ttggaagtaa aattta

```

```

<210> 95
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (396)
<223> n = A,T,C or G

```

<400> 95

cctccacccc	ncttanttca	tgagattcga	naatgncact	tntgtgctnt	ttnctnnttn	60
tattctnaen	atttctttct	tggngecgna	nnaateccnt	ttttnnnggc	gnctctccen	120
ncttntnntt	tcntggngct	ntcccttttc	nnnnnaaact	tntacnnngt	ttanaantnt	180
ttctgnangg	gggnntccna	aananttttt	ccnctnccct	nattecnctc	tnaannctcn	240
cnaattgttt	ccccccccc	ntagnntatt	ttttctaaaa	aattaactcc	nacgganaaa	300
attttcccta	aaatttcncc	tccanatttn	gaaaaaacnc	gcccgganct	nntntncgaa	360
tntnaatttt	tnaaaaaaan	ttattttcat	cnngnn			396

<210> 96

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 96

cctgggtacc	aaatttcttt	atttgaagga	atggtacaaa	tcaaagaact	taagtggatg	60
ttttggacaa	cttatagaaa	aggtaaagga	aaccccaaca	tgcatgcact	gccttggcga	120
ccagggaagt	cacccacg	ctatggggaa	attagccga	ngcttaactt	tcattatcac	180
tgcttccaag	ggngtgcttg	gcaaaaaaat	attccgcaa	ccaaatcggg	cgctccatct	240
tgcccagttg	gtncgggnc	cccaattctt	ggatgcttct	ncctcttntt	ccggaatgng	300
ctcatgaant	cccccaanng	gggcattttg	ccagnggcn	tttngccatt	cnagnnggcc	360
tgatccattt	tttccaatgt	aatgccnctt	cattgn			396

<210> 97

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 97

ctcacctcc	tentnntnt	canaatattg	ngaactnnt	nctgntcgaa	tcactggcat	60
taaagganca	ctagctaattg	gcactaaatt	tacnnactan	ggaaactttt	ttataatant	120
gcaaaaacat	ntnaaaaaga	ntgnagtctg	cccatttctg	cttnggaaga	nctcttcaact	180
tntaancccn	natgnngncc	tttgggtcaa	aanctccg	attattacng	ngttneccnc	240
tatttgnctt	tcctttntcc	ccaangcnc	anatttcnna	actttncnt	naaatgcctt	300
tatttnatnn	entttcnacn	ncttaanntt	ccctttnaan	aangatccct	ncttcaaatn	360
ntttccngt	tcctngcatt	ncccnnnnat	ttctct			396

<210> 98

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 98

acagggacaa tgaagccttt gaagtgccag tctatgaaga ggccgtggtg ggactagaat	60
cccagtgccg cccccaagag ttggaccaac caccacctac agcactgttg tgataccccc	120
agcacctgan gaggaacaac ctaccatcca gaggggccag gaaaagccaa actggaacag	180
aggcgaatgg ctacagagggg tncatggcca agaaggaagc cctggaagaa cttcaatcac	240
cttcggtttc gggaccaccg gcttgtgtcc ctgttctgac tgcanaactt ggcgngtnc	300
cccattanaa cctntgactc nnccttgcgt ataagncgtt tttggcccct gatgatgata	360
gggtttttat gangacactt gggcaccccc ttaatg	396

<210> 99

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 99

ntnttttttc cgncnaaagg gcaagngttt ncatctttcc tgnccncnca ananngggtn	60
tntgtgcntt tnttttttcc caaaaccggg gtnggggaca ccttttgagg anccactnnt	120
cntccggggc nnnnttttag aaggngncta anaagcntct tgnnggggga aaaacatctt	180
tttgcncncc acataccccc aagggggggg ggtgtctggg agganactaa ngacttttnt	240
tttttnnccn caaanaactg anggccccca ttgctcccc cccantcttt aaaaaacccc	300
ttcaatttcc ttgncnggna aaaanggttg gnaaaaaang agngngcntc nnttncnttt	360
natggaaggn aaaaggtttt tggttgnaaa accccg	396

<210> 100

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 100

ctaacacggt gaaaccctgt ctctactaaa aatacaaaaa aattagccag gcgtggtggc	60
gggcacctgt agtcccagct gctcaggaag ctgaggcagg agaatggcgt gaaccagaa	120
ggcggagctt gcagtgcgt gagatcgtgt cagtgcactc cagcctgggc gacagagcga	180
gactcccgtt caaaaaaaaa aaaaaaaaaa gaaaagaaaa agctgcagng agctgggaat	240
gggccctatc ccctccttgg ggatcaatga gacccctttt caaaaanaaaa aaaaaataa	300
tgngattttg gnaacatatg gcactggtgc ttcnnggaat tctgtttntn ggcattgnccc	360
cctntgactg nggaaaaatc cagcaggagg cccana	396

<210> 101

<211> 396

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 101
 agttataact caacagttca tttatatgct gttcatttaa cagttcattt aaacagttca 60
 ttataactgt ttaaaaatat atatgcttat agncaaaaann tgggtgtggcg nagttgttgc 120
 cgcttatagc tgagcattat ttcttaaatt cttgaatggt cttttggngg gntnctaaaa 180
 ccgtatatga tccatttttna tgggaaacng aattcntnnc attatcnac cttggaaata 240
 cnnaacgtgg gggaaaaaaa tcattccnc cntccaaaac tatacttctt ttatctngan 300
 nttcttgntc ctgencnggt ttngaata nctgggcaaa nggntttnc aaatcctnt 360
 acnntncttt gggaantanc ggcaantent cncctt 396

<210> 102
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 102
 actatacata agaacangct cacatgggag gctggagggt ggtacccagc tgctgtggaa 60
 cgggtatgga caggtcataa acctagagtc agngtctgt tggcctagcc catttcagca 120
 ccctgccact tggagnggac ccctctactc ttcttagcgc ctaccctcat acctatctcc 180
 ctntctcccat ctctacgga ctggcgccaa atggctttcc tgccaatttt gggatcttct 240
 ctggctctcc agcctgctta ctctctatt tttaaagggc caaacaatc cttctcttt 300
 ctcaaacaca gtaatgnggc actgacccta ccacaccta tgaagggggc ttgttgcttt 360
 tatttgggcc cgatctgggg ggggcaaaat attttg 396

<210> 103
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 103
 ttgtgttggg actgctgata ggaagatgct ttcaggaaat gctaaaattg ggcaccctgc 60
 cccaacttca aagccacagc tggtagcca natggtcagg ttaaagatat caacctgctg 120
 actacaaagg aaaatatggt ggggtcttct tttaccctct tgacttccct ttgngngccc 180
 ccgaganca ttgctttccg ngatagggca aaanaaatta aaaaacttaa ctggccagtg 240
 aatggggctt ctgnggatct cttcttgga ttacatnggc aatccctaaa aaacaagang 300
 actgggaccc ataacattct tttgnatcaa ccgaagcccc cattgttang atatngggct 360
 taaangctga tnaagcatct cgtccgggcn ttttat 396

<210> 104
 <211> 396
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)... (396)

<223> n = A,T,C or G

<400> 104

aagggagggc gcgccaagac cttcccactc gngcacactg ggggcgcca cangacgcaa	60
cccagtccaa cttggatacc cttggnttta gttctcggac acttctttta tctctccgtc	120
gcaacttgtc aagttctcaa nactgtctct ctgngntatc tttttcttc gctgctcttc	180
nnccccgcac gtattnttca aaangtctgc aattgttgna tacntnganc tncaccactg	240
ttacnaggtc atnaatttcn cntcaactct ntncncttg ttcctgata tntcggccgg	300
ngnnccaat tctgtatttt nctentcaac gntctcactt ttnectctc cnggccactt	360
tctccccttc cttattccgg cnttgtttgc cncat	396

<210> 105

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)... (396)

<223> n = A,T,C or G

<400> 105

tcaatagcca gccagtgttc atttttatcc ttgagctttt agtaaaaact tectggnttt	60
atttttagtc attgggtcat acagcactaa agtctgctat ttatggaaac taactttttt	120
gtttttaactc caggccaaca tgtatgtaaa ttaaattttt agataattga ttatctcttt	180
gtactacttg agatttgatt atgagatgtg catattgctt tgggaagagc tcgaggaagg	240
aaataattct ctcttttggg ttgaacctca actagataaa ccctaggaat tgtaactgc	300
acaagnattt tcattccaca aaacctgagg cagctctttt gccagagcgt tectgnaccc	360
ccccaccca cttgccttgg gtctttanaa ngagcc	396

<210> 106

<211> 396

<212> DNA

<213> Homo sapien

<400> 106

gctgtgtagc acactgagtg acgcaatcaa tgtttactcg aacagaatgc atttcttcac	60
tccgaagcca aatgacaaat aaagtccaaa ggcattttct cctgtgctga ccaaccaa	120
aatatgtata gacacacaca catatgcaca cacacacaca cacaccaca gagagagagc	180
tgcaagagca tggaattcat gtgtttaaag ataatccttt ccatgtgaag tttaaaatta	240
ctatatattt gctgatggct agattgagag aataaaagac agtaaccttt ctcttcaaag	300
ataaaatgaa aagcaattgc tcttttcttc ctaaaaaatg caaaagattt acattgctgc	360
caaatacttt caactgaaaa gaacagtatt gctttg	396

<210> 107

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 107
 ttcacagaac anggtggttt attattttcaa tagcaaagag ctgaaaaatg tcgggtccca 60
 taaaggagca gaacctgacc cagagcctgc agtacatttc caccacacag ggggtgcaggc 120
 tgggccaggc agggccaaag gcagcagaaa tgggagtaag agactgtgcc cactgagaag 180
 ctctgctggg tgtgggcagg tgggcatgan atgatgatga tgtagtgtaa ggaccaggta 240
 ggcaaaacct gtcaggnttg ntgaatgtca nagtggatcc aaaaggctga gggggtcgtc 300
 anaaggccgg nggncccncc cttgcccgta tgggccttca aaaagtatgc ttgctcatcc 360
 gttgttttnc ccanggagct gccanggana aggctn 396

<210> 108
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 108
 gcctgctttt gatgatgtct acagaaaatg ctggctgagc tgaacacatt tgcccaattc 60
 cagggtgtga cagaaaaccg agaatattca aaattccaaa tttttttctt aggagcaaga 120
 agaaaatgtg gccctaaagg ggggttagttg aggggtaggg ggtagtgagg atcttgattt 180
 ggatctcttt ttattttaat gtgaatttca acttttgaca atcaaagaaa agacttttgt 240
 tgaaatagct ttactgttc tcacgtgttt tggagaaaaa natcancct gcaatcactt 300
 tttgnaactg nenttgattt tngcncca agctatctn aatctgtct gngtanaaaa 360
 tgnccctggnc ttttgaanga atacatgngt gntgct 396

<210> 109
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 109
 ggccgtaggc agccatggcg ccagcccg aatggcatgg tcttgaagcc ccacttccac 60
 aaggactggc agcggcgcggt ggccacgtgg ttcaaccagc cggcccgga gatccgcaga 120
 cgtaaggccc ggcaagcaa ggcgcgccgc atcgctccgc gcccgcgtc ggggtccatc 180
 cggcccatcg tgcgtgccc acggttcggt accacacgaa gggcgcccg gcgcgnttc 240
 agcctggaag agctcagggt ggccggattt acaagaagng gccngacatc ngattcttg 300
 ggatnccnga agnggaacaa gtcacngagt ccttgacgcc acntcagcgg ntgatgacac 360
 cgttccnaact catctnttcc caagaaacct cngnnc 396

<210> 110
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 110
 nntgggctcc tnncantnat aataaacng actcatacnc cacaaggaga tgaacaggan 60
 tatgtncatn ctgacgcgga aacagngcan ggagctgagg agnggccaag atgagaccta 120
 nnggccnngg tgggcgcatt cccggnggag ggggccacta aggantacga nnntcnagcg 180
 gctcttgng gcnncctcc tcacnctgn ntattcgatt gtcnncnatg ncntcctatn 240
 atnntcanna ttctntnntn atctentnta cnnentcnen ttcatgntta cngntccctc 300
 tcnttctnac cntntctgn anctccttcc tnnncttcc atctntnttc ngctttcttt 360
 cttnaatcnt nntttaacnt nntctncttt ntnatt 396

<210> 111
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 111
 taangancat nctggntnt gctnnccgn ctnattgant gttaaaggca attntgtggn 60
 tgtcccagng aatgncggct nattttcttt ccacattgng cncattcact cctcccactc 120
 ttggcatgtn gngacataag canggtacat aatngnaaaa atctgnattt ctgatgccan 180
 angggtnan cntnttgnat ntcattccat tgatatacag ccactntttt atttttgatc 240
 ancggccttc ggntcactgc ncanggtact tgacctcagt gtcactatta tgggntttgg 300
 tttcncctct ttncnggcn ttntntttcn cacnttncan cttntctnnt nnaaaannna 360
 nncactctct cttgctctct ngatacnng tctnaa 396

<210> 112
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 112
 tcaacgtcac caattactgc catttagccc acgagctgcg tctcagctgc atggagagga 60
 aaaaggtcca gattcgaagc atggatccct ccgccttggc aagcgaccga tttaacctca 120
 tactggcaga taccaacagt gaccggctct tcacagtga cgaatgttaa gntggaggct 180
 ccaagnatgg tatcatcaac ctgcaaagtc tgaagacccc tacgctcaag gtgttcatgc 240
 acgaaaacct ctacttcacc aaccggaagg tgaattcggg gggctgggccc tcgctgaatc 300
 acttggtatc cacattctgc tatgcctcat gggactcgca gaacttcagg ctggccaccc 360
 tgcctccacc atcactgntn gncaatantc acccag 396

<210> 113
 <211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 113

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nnnnntnnnn nggagcctta atttcagagt tttattgtat tgcactaaag gaacagcagg      60
atggntatac aattttctct cattcagttt tgaaaatctg tagtacctgc aaattcttaa      120
gaataccttt accaccagat tagaacagta agcataataa ccaatttctt aataagtaat      180
gtcttatacaa taaaaacaca tttaaaatag ctttaaattgc attcttcaca agtaattcag      240
catatatattt atatcatggt tactttatgct tangaattnn agcaggatnt ttattctttt      300
gatggaaata tgggaaaact ntattcatgc atatacangg ataattattca gcgaaggga      360
aatcccgctt ttattttggn aatgattcat atataa

```

<210> 114

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 114

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aaatgggaca acgtgattct tttgttttaa ataaatactn agaacacgga cttggctcct      60
acaagcattt ggactctaag gnttagaact ggagagtctt acccatgggc ccncncagg      120
gacgccacgg ttccctccca ccccgngatc aagacacgga atcngntggc gatngttgga      180
tcgcnatgtg ccccttatct atagccttcc cnggncatnt acangcagga tgcggntggg      240
anaactacaa ctgnaatntc tcnaacggtg atgggtccca ccgatnaaga ttctacctng      300
tcttttctnc ccttgagtg tgagtgnnng aggaagaagc ccttncctta catcaccttt      360
tgnacttctg aacaaganca anacnatggc ccccc

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<210> 115

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 115

```

ccgcctgggt cggccgcct gcctccactc ctgcctctac catgtccatc agggtgaccc      60
agaagtcceta caaggtgtcc acctctggcc cccgggcctt cagcagccgc tcctacacga      120
gtgggcccgg ttcccgcatc agctcctcga gttctccccg agtgggcagc agcaactttc      180
gcggtggcct ggcggcggtc atggtggggc cagcggcatg ggaggcatca cccgcagtta      240
cggcaaccag agcctgctga gcccttgcc tggaggngga cccaacatc aagccgngcg      300
caccacaggaa aaggagcaga ncaagaccct caacaacaag nttgcttctt catagacaag      360
ggaccgggtc ttgaacagca naacaagatg ntggag

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<210> 116
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 116
 atctcagttt actagctaag tgactttggg caagggattt aacctctcgt ccctcagttt 60
 cctcctatgt aaaatgacaa ggataatagt accaacccaa tgtagattaa atgagtttac 120
 gaagtgttag aatagtgcctt ggcacattag tgctttacaa ctgctatttt gattgttggt 180
 gtgggctctc tcaaatgcat tgtctctaga tgccagtgc ccaggtcaaa atttaccttt 240
 aaccaagctg catgtttccc agactgntgc acagtcctct accctgagan aaagcttcca 300
 cccaaggata cttttacttt ctgctggaaa actgatgagc aanggaaca ngggacactt 360
 atcgccaact ggaaangaga aattcttctt tttgct 396

<210> 117
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 117
 aaacattttt taataaaatt cctatagaaa gctcagtcac agggcaaata ctgagttctc 60
 ttcccatat caccgaggat tgagagctcc caatattctt tggagaataa gcagtagttt 120
 tgctggatgt tgccaggact cagagagatc acccatttac acattcaaac cagtagttcc 180
 tattgcacat attaacatta cttgccccta gcaccctaaa tatatggnac ctcaacaaat 240
 aacttaaaga ttcccggtgg ggcgcanacc atttcaattt gaactaatat ccttgaaaaa 300
 aatcacatta ttacaagntt taataaatat nggaagaaga gctggcattt ttctaanaac 360
 tgaattenga cttggnntta ttccataaat acggtt 396

<210> 118
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 118
 accnnacact gntnnntttt aacnattaca acttctttat atggcagttt ttactgggng 60
 cctaacactc tctttactgn ctcaagnnga agtccaaaca aatttcattt ttgtagtaaa 120
 aaatctttat ttccaaaatg atttgttagc caaaagaact ataaaccacc taacaagact 180
 ttggaagaaa gagacttgat gcttcttata aattcccat tgcanacaaa aaataacaat 240
 ccaacaagag catggtaccc attcttacca ttaacctggn tttaannctc caaanncnnga 300
 tttaaaaatg accccactgg gcccaatcca acatganacc taggggggnt tgccttgatt 360

angaatcccc cttanggact ttatctnggc tganaa 396

<210> 119

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 119

atggccagct cactttaaat accacctcaa gactcatcga aatgaccgct ccttcatctg	60
tcttgcagaa gggtgtggga aaagcttcta tgtgctgcag aggctgaagg tgcacatgag	120
gacccacaat ggagagaagc cctttatgtg ccatgagtct ggctgtggta agcagtttac	180
tacagctgga aacctgaaga accaccggcg catccacaca ggagagaaac ctttcctttg	240
tgaagcccaa ngatgtggcc gtcccttctg gagtattcta ncttcgaaaa catctggngg	300
ntactcanga gagaaagcct cattantgcc antctgnggg aaaaccttct ntcagagngg	360
angcaggaat gtgcatatta aaaagctncc ttgnac	396

<210> 120

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 120

catgggtcag tcggctctga gagttcgaag agggcacatt cccaaagaca ttcccagtca	60
tgaaatgtag aagactggaa aattaagaca ttatgtaaaag gtagatatgg cttttagagt	120
tacattatgc ttggcatgaa taagggtcca ggaaaacagt ttaaaattat acatcagcat	180
acagactgct gttagaagggt atgggatcat attaagataa tctgcagctc tactacgcat	240
ttattgttaa ttgagttaca nangncattc annactgagt ttatagancc atattgctct	300
atctctgngn agaacatttg attccattgn gaagaatgca gttttaaata tctgaatgcc	360
atctagatgt attgtaccna aaggggaaaa ataaca	396

<210> 121

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 121

tttttttttt ttttttttaa aatcaagtta tgtttaataa acattaataa atgtttactt	60
aaaagggtta ataaacnttt actacatggc aaattatttt agctagaatg cttttggctt	120
caagncatan aaaccagatt cnaatgccct taaanaattt tnaaanatcc attgangggg	180
ataactgtaa tccccagggtt gaanagggtt gggtatgaca ggtacanggg gccagcccg	240

```

tnntnncana nncagactct tacntcttt ctgctgtgnc accctcaggc attggtccca    300
ttctcngggg tgcncatggg aagatggctt tggaentaac nacacccttt tgtncacgta    360
aaggccngat gcagggtcaa anagnttccn ccatnt                                396

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<210> 122

<211> 396

<212> DNA

<213> Homo sapien

<400> 122

```

gtcgacatgg ctgccctctg ggctcccaga acccacaaca tgaaagaaat ggtgctaccc    60
agctcaagcc tgggcctttg aatccggaca caaaaccctc tagcttggaa atgaatatgc    120
tgcactttac aaccactgca ctacctgact caggaatcgg ctctggaagg tgaagctaga    180
ggaaccagac ctcatcagcc caacatcaaa gacaccatcg gaacagcagc gcccgcagca    240
cccaccccg cccggcgact ccatcttcat ggccaccccc tgcggtggac ggttgaccac    300
cagccaccac atcatccag agctgagctc ctccagcggg atgacgccgt cccaccacc    360
tccctcttct tctttttcat ccttctgtct ctttgt                                396

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<210> 123

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 123

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gccctttttt tttttttttt tttcttagtg ccaggtttat tccctcacat gggtggttca    60
catacacagc acanaggcac gggcaccatg gganagggca gcactcctgc cttctgaggg    120
gatcttggcc tcacggtgta anaagggana ggatggttct tcttctgccc tcaactaggc    180
ctagggaaac cagnagcaaa tcccaccagc ctttccatnt ctcagccaag ganaagccac    240
cttggtgacg tttagttcca accattatag taagtggana agggattggc ctggtcccaa    300
ccattacagg gtgaanatat aaacagtaaa ggaanatata gtttgatga ggccacagga    360
aggagcanat gacaccatca aaagcatatg caggga                                396

```

<210> 124

<211> 396

<212> DNA

<213> Homo sapien

<400> 124

```

gaccattggc ccagacctgg aagatataac attcagttcc caccatctga ttaaaacaac    60
ttctccctt acagagcata caacagaggg ggcacccggg gaggagagca catactgtgt    120
tccaatttca cgcttttaat tctcatttgt tctcacacca acagtgtgaa gtgctggtga    180
taatctccat ttcaaaacca aggaagcagc ctcagagtgg tcgagtgaac cacctcacgc    240
aggctgagtc cagagcttgt gtcctcttg attcctgggt tgactcagtt ccaggcctga    300
tcttgctgt ctggctcagg gtcaaagaca gaatggtgga gtgtagcctc cacctgatat    360
tcaggctact cattcagtc caaatatgta ttttcc                                396

```

<210> 125

<211> 396

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 125
 cccttttttt tttttttttt tttttttttt ttttttactt tgnaaacaaaa atttattagg 60
 attaatgcaa attaaaaaac ttcatgcnc ncncttgct ataattacct gaaatgacaa 120
 agttatactt agcttgagng naaaacttgn gccccaaaaa ttntgtttgg aaagcaaaaa 180
 aataattgat gcncatagca gngggcctga tnccnccaca gngaattgtg ttaaggnc 240
 aacaaacagg ggncaaaaa gcatacatta cttttaagct ttgggnccaa ggaaaangtc 300
 attccctacc tccttcaaaa gcaaaactcat natagcctgg gchcctaggn ctggagcctn 360
 ttttttcgag tctaanatga acatntggat ttcaan 396

<210> 126
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 126
 cgcgctcgact cgcaagtgga atgtgacgtc cctggagacc ctgaaggctt tgcttgaagt 60
 caacaaaggg cagcaaatga gtcctcaggt ggccaccctg atcgaccgct ttgtgaaggg 120
 aagggggccag ctagacaaag acaccctaga caccctgacc gccttctacc ctgggtacct 180
 gtgctccctc agccccgagg agctgagctc cgtgcccccc agcagcatct gggcggtcag 240
 gccccacgac ctggacacgc tggggctacg gctacagggc ggcattccca acggctacct 300
 ggtcctagac ctcagcatgc aagaggccct ctcggggacg ccctgcctcc taggacctgg 360
 acctgttctc accgtcctgg cactgctcct agcctc 396

<210> 127
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 127
 tttttttttt ttgnggtaa aatgcaaatg ttttaaaata tgtttatatt gtatgtttta 60
 caatgaatac ttcagcaaag aaaataatta taatttcaaa atgcaatccc tggatttgat 120
 aaatatcctt tataatcgat tacactaatc aatatctaga aatatacata gacaaagtta 180
 gctaataaat aaaataagta aaatgactac ataaactcaa tttcagggat gagggatcat 240
 gcatgatcag ttaagtcact ctgccacttt ttaaaataat acgattcaca tttgcttcaa 300
 tcacataaac attcattgca ggagttacac ggctaatacat tgaaaattat gatctttgtt 360
 agcttaaaag aaaattcagt ttaatacaaa gacatt 396

<210> 128
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 128

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gccctttttt ttttttttta aaggcaaata aaataagttt attgggatgt aaccccatca      60
taaattgagg agcatccata caggcaagct ataaaatctg gaaaatttaa atcaaattaa      120
attctgcttt taaaaagggtg ccttaagtta accaagcatt ttgataacac attcaaattt      180
aatatataaa aatagatgta tcctggaaga tataatgaan aacatgccat gtgtataaat      240
tcanaatacg ctttttacac aaagaactac aaaaagttac aaagacagcc ttcaggaacc      300
acacttagga aaagtgagcc gagcagcctt cacgcaaagc ctcttcaaa naagtctcac      360
aaagactcca gaaccagccg agtntgtgaa aaagga                                396

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<210> 129

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 129

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gccctttttt tttttttttt ttttactcag acaggcaata tttgctcaca tttattctct      60
tgcacgtaa atagtagcca actcacaaaa ataaagtata caanaatgta atatttttta      120
aaataagatt aacagtgtaa gaaggaaaat ctcaaaaaaa gcanatagac aatgtanaaa      180
attgaaatga aatccacag taanaaaaaa aaaacanaaa agtgcctatt taanaattat      240
gctacatgtg gaacttaact agaccatttt aanaaagacc aatttctaata gcaaattttc      300
tgagggtttc anattttatt tttaaaatat gttatagcta catgttgtcn acnccggccgc      360
tcgagtctan agggcccgtt taaacccgct gatcag                                396

```

<210> 130

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 130

```

cgcccttttt tttttttttt tanngnacgt gnetttatct ctggatgata taaaanaaaa      60
aacttaaaaa acaccccaaa ccaaacacca atggatcccc aaagcgatgt gactccctct      120
tcccaccggg ataaatagag acttctgtat gtcagtctac cctcccgccc ccataacccc      180
ctctgctata nacatactct gggatatatat tactctactc ggcaatagac atctcccgaa      240
aatagaattc ctgccctgac acctgactct tccctggccg catcanacca cccgccactg      300
tagcacactg gtgtccttgc cccctgtggt cagggccatg ctgtcatccc acaanaaggc      360
cacatttgtc acatggctgc tgtgtccacc gtactt                                396

```

<210> 131

<211> 396

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 131
 gccctttttt tttttttttt tttttttttt ttcagtttac acaaaaacnc ttttaattgac 60
 agtatacnnt ttccaaaat atnttttngt aaaaaaatgc aataattatt aactatagtt 120
 ttacaaaaca agtttntcan taaattccag tgncttnaa accccnnncn annaaaacat 180
 atatganccc ccagttcctg ggcaaaactgt tgaacattca ctgcanacaa aaagaccanc 240
 nccaaanagt catctgngnc ctccatgctg ngtttgacc aaacctgagg gancagctag 300
 ngaccgtgac aaaagctntg ctacagtttt actntngccc tntntgcctc ccccatnatg 360
 tttccttggg ccttcantcc tgtnggagta agttcc 396

<210> 132
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 132
 cgcgctcgacc ggggccgtag cagccgggct ggtcctgctg cgagccggcg gcccgaggagtg 60
 gggcgggcgt atgtaccttc cacattgagt attcagaaaag aagtgatctg aactctgacc 120
 attctttatg gatacattaa gtcaaataata agagtctgac tacttgacac actgggctcgg 180
 tgagttctgc tttttctttt taatataaat ttattatggt ggtaaattta gcttttggct 240
 tttcactttg ctctcatgat ataagaaaat gtaggttttc tctttcagtt tgaattttcc 300
 tattcagtaa aacaacatgc tagaaaacaa acttttggaa aggcattgta actatttttt 360
 caaatagaac cataataaca agtcttgtct taccct 396

<210> 133
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 133
 ntattacccc tectggnnan ntggnnatan nctgcaaggn gatnnncccg nngaacttca 60
 ctgatnnncc aatnaaaact gctttaaanc tgactgcaca tatgaattnt aatacttact 120
 tngcgggagg ggtggggcag ggacagcaag ggggaggatt gggaanacaa tagacaggca 180
 tgctggggat gcngcgggct ctatggcttc tgangcgnaa agaaccagct ggggctctag 240
 ggggtatccc cagcgccct gtagcngcnc attaaacgag gcgggtgtgg nggttacttc 300
 gcaaagngac cgatncactt gccagcgccc tagctgccc ctccttngc tttcttcctt 360
 tcctttctcg ccacnttnnc cggctntccc cgncaa 396

<210> 134
 <211> 396
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 134

tttttttttt	ttctgctttt	tatatgttta	aaaatctctc	attctattgc	tgctttattt	60
aaagaaagat	tactttcttc	cctacaagat	ctttattaat	tgtaaaggga	aaatgaataa	120
ctttacaatg	ganacacctg	gcanacacca	tcttaaccaa	agcttgaagt	taacataacc	180
agtaatagaa	ctgatcaata	tcttgtgcct	cctgatatgg	ngtactaana	aaaacacaac	240
atcatgccat	gatagtcttg	ccaaaagtgc	ataacctaaa	tctaatacata	aggaaacatt	300
anacaaactc	aaattgaagg	acattctaca	aagtgccttg	tattaaggaa	ttattcanag	360
taaaggagac	ttaaaagaca	tggcaacaat	gcagta			396

<210> 135

<211> 396

<212> DNA

<213> Homo sapien

<400> 135

gcgtcgacgc	tggcagagcc	acaccccaag	tgctgtgtcc	cagaggggctt	cagtcagctg	60
ctcactcctc	cagggcactt	ttaggaaagg	gttttttagct	agtgtttttc	ctcgctttta	120
atgacctcag	ccccgcctgc	agtggctaga	agccagcagg	tgcccatgtg	ctactgacaa	180
gtgcctcagc	ttcccccccg	cccgggtcag	gccgtgggag	ccgctattat	ctgcgtttctc	240
tgccaaagac	tcgtgggggc	catcacacct	gccctgtgca	gcggagccgg	accaggctct	300
tgtgtcctca	ctcaggtttg	cttccccctg	gccactgtct	gtatgatctg	ggggccacca	360
ccctgtgccg	gtggcctctg	ggctgcctcc	cgtggt			396

<210> 136

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 136

ttatgcttcc	ggctcgtntg	ttgtgtggaa	ttgtgagcgg	ataacaattt	cacacaggaa	60
acagctatga	ccatgattac	gccaaagtat	ttaggtgaca	ctatagaata	ctcaagctat	120
gcatcaagct	tggtaccgag	ctcggtacca	ctagtaacgg	ccgccagtgt	gctggaattc	180
gcggncgntc	nantctagag	ggcccgttta	aaccgcgtga	tcagcctcga	ctgtgccttc	240
tagttgccag	ccatctgttg	tttgcccctc	ccccgtgcct	tccttgaccc	tggaagggtg	300
cactcccact	gtcctttcct	aataaaatga	ggaaattgca	tcgcattgtc	tgagtaggtg	360
tcattctatt	ctgggggggtg	gggtggggca	ggacan			396

<210> 137

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 137
 tttttttttt ttctgctttg tacttgagtt tatttcacaa aaccacggag aaagatactg 60
 aaatggagct ctttccagcc tccaagcaag gagggcccag cagccagctc ccagcccctt 120
 gagccctttt tgtaggccc acacccaaaa gagganaacc agtgtgtgcg cgaagggtaca 180
 tggcaaggca cttttgaaaa catcccagtt taccngggtg aaattgaact tactctgaaa 240
 cagatgaaaa gggacatgca aaattgctga gcacatggag gtgtttgtta gtaggtgaaa 300
 atcatgtcct ggggtataacc cagcttctcc aggttagggg gagccgcctg ctggatcagt 360
 ggtggcgggc cacacaccag gatgagcgtg gacttc 396

<210> 138
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 138
 cccttttttt ttttttttac aaatgagaaa aatgtttatt aagaaaacaa tttagcagct 60
 ctccctttana attttacaga ctaaagcaca acccgaaggc aattacagtt tcaatcatta 120
 acacactact taaggngctt gcttactcta caactggaaa gttgctgaag tttgtgacat 180
 gccactgtaa atgtaagtat tattaaaaat tacaaattgt ttgggtgatta ttttgatgac 240
 ctcttgagca gcagctcccc ccaanaatgc ancaatggta tgtgggtcac cagctccata 300
 tcggcaaaaat tcgtggacat aatcatcttt caccattaca gataaaccat attcctgaag 360
 gaagccagtg agacaagact tcaactttcc tatatc 396

<210> 139
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (396)
 <223> n = A,T,C or G

<400> 139
 ccgccctttt tttttttttt ttcacaaaag cactttttat ttgaggcaaa nagaagtctt 60
 gctgaaagga ttccagttcc aagcagtcaa aactcaaccg ttagnngcac tattttgacc 120
 tgggtanattt tgcttctctt tgggtcanaaa aggggtattca ggttgactt tccccagcag 180
 ggtaaaaaaga agggcaaaagc aaactggaan anacttctac tctactgaca gggctnttga 240
 natccaacat caagctanac acnccctcgc tggccactct acaggttgct gtccactgc 300
 tgagtgcac aggccatact acatttgcaa ggaaaaaaat gaggcaanaa acacaggtat 360
 aggtcacttg gggacgagca ggcaaccaca gcttca 396

<210> 140
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 140
 tttttttttt tttttttttt tttttttctc atttaacttt tttaatgggn ctcaaaattn 60
 tgngacaaat ttttgggtcaa gttgtttcca ttaaaaagtn ctgattttta aaactaataa 120
 cttaaaactg ccncncccaa aaaaaaaaaac caaaggggtc cacaaaacat tntcctttcc 180
 ttntgaaggn tttacnatgc attgttatca ttaaccagtn ttttactact aaacttaaan 240
 ggccaattga aacaaacagt tntganaccg ttnttcncc actgattaaa agnggggggg 300
 caggtattag ggataatatt catttancct tntgagcttt ntgggcanac ttggngacct 360
 tgccagctcc agcagccttn ttgtccactg ntttga 396

<210> 141
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 141
 acgccgagcc acatcgctca gacaccatgg ggaaggtgaa ggtcggagtc aacggatttg 60
 gtgcgtattgg gcgcctggtc accagggctg cttttaactc tggtaaagtg gatattgttg 120
 ccatcaatga ccccttcatt gacctcaact acatggttta catgttccaa tatgattcca 180
 cccatggcaa attccatggc accgtcaagg ctgagaacgg gaagcttgtc atcaatggaa 240
 atcccatcac catcttcag gagcgagatc cctccaaaat caagtggggc gatgctggcg 300
 ctgagtacgt cgtggagtc actggcgtct tcaccacat ggagaaggct ggggctcatt 360
 tgcagggggg agccaaaagg gtcacatct ctgccc 396

<210> 142
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 142
 acgcaggaga ggaagcccag cctgttctac cagagaactt gccaggtca gaggtctgcg 60
 tagaagccct tttctgagca tcctctctc tcctcacacc tgccactgtc ctctgcgttg 120
 ctgtcgaatt aaatcttgca tcaccatggg gcacttctgt ggcctactca ccctccaccg 180
 ggagccagtg ccgctgaaga gtatctctgt gagcgtgaac atttacgagt ttgtggctgg 240
 tgtgtctgca actttgaact acgagaatga ggagaaagt cctttggagg ccttctttgt 300
 gttcccatg gatgaagact ctgctgttta cagctttgag gccttggtgg atgggaagaa 360
 aattgtagca gaattacaag acaagatgaa ggcccc 396

<210> 143
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 143
 tttttttttt tttccatana aaataggatt tattttcaca ttttaaggnga acacaaatcc 60

atgttccana aatgttttat gcataacaca tcatgagtag attgaatttc tttaacacac	120
anaaaaatca aagcctacca ggaaatgctt ccctccggag cacaggagct tacaggccac	180
ttntgttagc aacacaggaa ttcacattgt ctaggcacag ctcaagngag gtttgttccc	240
aggttcaact gctcctaccc ccatgggccc tcctcaaaaa cgacagcagc aaaccaacag	300
gcttcacagt aaccaggagg aaagatctca gngggggaac cttcacaaaa gccctgagtt	360
gtgtttcaaa agccaagctc tggggtctgn ggctg	396

<210> 144

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 144

tttttttttt tttcgtctctt tgggtctgaca agaaaagagt tttaggtgtg tgaagtaggg	60
tgggaaaaaa ggtcagtttc aaattcagta acatatggta acactaagtt aggctgctgc	120
attcttttct ttgggtactt aagccagctg gcacttccac tttgtaacca attatattat	180
gatcaacaac taatcagtta gttcctcagc ttcaactgaa nagttcctga ttacctgatg	240
aaggacatac ttgctctggc ttcaattagc atgctgtcaa gcateccctct ccatgcttaa	300
catggcaaca caaaacccaa gagtccttct ntttttttca ttagccatga ataaacactc	360
acaaagggga agagtagaca ctgcttttag taaacg	396

<210> 145

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 145

tttttttttt tttttttcaa tggatccggt agctttacta ctaanatctt gctganatca	60
nanaagggct tctgggcagg ctgagcactg ggggtgtgca acatggtaac tctgaataan	120
anaaaccttg agttttactg ggcaanaaaa naacaagngg taggtatgat ttctgaacct	180
ggaaatagcg aaaatgaagg aaattccaaa agcgcgtatt tccaaataat gacaggccag	240
caagaggaca ccaaacctnt anaaagaggt attntttctt ccagctactg atggctttgg	300
catccacag gcacattcct ttggccttca ggatcttana tgcanatgtg ganagtcaag	360
aggtaggctg actctgagtc ttcagctaaa ttcttt	396

<210> 146

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 146

tttttttttt	ttttcattag	caaggaagga	tttatttttt	cttttgaggg	gagggcggaa	60
cagccgggat	ttttggaaca	ctacctttgt	ctttcacttt	gttgtttg	tgtaacacn	120
aataaatcan	aagcgacttt	aaatctccct	tcgcaggact	gtcttcacgt	atcagngcan	180
acaanaaac	agtggcctta	caaaaaanat	gttcaagtag	gctgcacttt	gcctctgngg	240
gtgaggcaca	ctgngggana	nacaaggtec	cctgnaacca	gagngggaa	ggacanagct	300
ggctgactec	ctgtctctcc	gcattctctc	ctccatgtgt	tttgaanagg	gaagcaacat	360
gttgaggtct	gatcatttct	acccagggaa	cctggt			396

<210> 147

<211> 396

<212> DNA

<213> Homo sapien

<400> 147

acggggaagc	caagtgaccg	tagtctcatc	agacatgagg	gaatgggtgg	ctccagagaa	60
agcagacatc	attgtcagtg	agcttctggg	ctcatttgct	gacaatgaat	tgctgcctga	120
gtgcctggat	ggagcccagc	acttccctaa	agatgatggg	gtgagcatcc	ccggggagta	180
cacttctctt	ctggctccca	tctcttcttc	caagctgtac	aatgaggtcc	gagcctgtag	240
ggagaaggac	cgtgaccctg	aggcccagtt	tgagatgcct	tatgtggtac	ggctgcacaa	300
cttcaccag	ctctctgcac	cccagccctg	tttcaccttc	agccatccca	acagagatcc	360
tatgattgac	aacaaccgct	attgcacctt	ggaatt			396

<210> 148

<211> 396

<212> DNA

<213> Homo sapien

<400> 148

acgtcccctg	attgttccag	accatgactc	ttcctgggtg	tgggtttgtt	acagagcagg	60
agaagcagag	gttatgacag	ttatgcagac	tttcccctc	ctttttctct	tttctcttcc	120
ccttgctttt	ccactgtttc	ttcctgctgc	cacctgggcc	ttgaattcct	gggctgtgaa	180
gacatgtagc	agctgcaggg	tttaccacac	gtgggagggc	agcccagtac	tgctccctctg	240
ccttccccac	tttgagaata	tggcagcccc	tttcattcct	ggcttggggg	aggggagacc	300
attgaagtag	aagcctcaaa	gcagactttt	ccctttactg	tgtgtactcc	aggacgaaga	360
aggaagatca	tgcttgatac	ttagattggt	tttccc			396

<210> 149

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 149

tttttttttt	tttaaagagt	cacattttat	tcaatgccta	tttgtacatg	ttactagcaa	60
taaactcttt	tatctttaat	tttgagaagt	tttacaata	cagcaaagca	gaatgactaa	120
tagagccggg	aaccaggaca	cagatttgga	aaaatagggtc	taattgggtg	ttacactgtg	180
tttatgtcat	acatttcgct	tatttttctc	aaanaaaaa	cagaatttat	aaaatgttaa	240
ttaaaaggaa	aacattctga	gtaaaatttag	tcccgtgttt	cttcctccaa	atctntttgt	300
tctacactaa	caggtcagga	taagtatgga	tggggaggct	ggaaaaaggg	catccttccc	360
catgcggtcc	ccagagccac	cctctccaag	caggac			396

<210> 150
<211> 396
<212> DNA
<213> Homo sapien

<400> 150
acgcctctct tcagttggca ccçaaacatc tggattggca aatcagtggc aagaagttcc 60
agcatctgga cttttcagaa ttgatcttaa gtctactgtc atttcagat gcattatatt 120
acaactgtat ccttggaat atatttctag ggagaatatt attgaagaaa atgttaatag 180
cctgagtcaa atttcagcag acttaccagc atttgatca gtggtagcaa atgaagccaa 240
actgtatctt gaaaaacctg ttgttccttt aaatatgatg ttgccacaag ctgcattgga 300
gactcattgc agtaatatatt ccaatgtgcc acctacaaga gagatacttc aagtctttct 360
tactgatgta cacatgaagg aagtaattca gcagtt 396

<210> 151
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)... (396)
<223> n = A,T,C or G

<400> 151
acaaaatgcc cagcctacag agtctgagaa ggaaatttat aatcaggtga atgtagtatt 60
aaaagatgca gaaggcatct tggaggactt gcagtcatac agaggagctg gccacgaaat 120
acgagaggca atccagcatc cagcanatga gaagttgcaa gagaaggcat ggggtgcagt 180
tgttccacta gtaggcaaat taaagaaatt ttacgaattt tctcagaggt tagaagcagc 240
attaagaggt cttctgggag ccttaacaag taccctatat tctcccacc agcatctana 300
gcgagagcag gctcttgcta aacagtttgc anaaattctt catttcacac tccggtttga 360
tgaactcaag atgacaaatc ctgccataca gaatga 396

<210> 152
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)... (396)
<223> n = A,T,C or G

<400> 152
acgcagcgt cggtctcctg gtaattcttc acctcttttc tcagctccct gcagcatggg 60
tgctggggcc tcttgctgc tcgccgccct cctgctgctt ctctccggcg acggcgccgt 120
gcgctgcgac acacctgcca actgcaccta tcttgacctg ctgggcacct gggcttcca 180
gggtgggtcc agcggttccc agcgcgatgt caactgctcg gttatgggac cacaagaaaa 240
aaaagtagng gtgtaccttc agaagctgga tacagcatat gatgaccttg gcaattcttg 300
ccatttcacc atcatttaca accaaggctt tgagattgtg ttgaatgact acaagtgggt 360
tgcctttttt aagtataaag aagagggcag caaggt 396

<210> 153
<211> 396

<212> DNA

<213> Homo sapien

<400> 153

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ccagagacaa cttcgcggtg tggatgaactc tctgaggaaa aacacgtgcg tggcaacaag      60
tgactgagac ctagaaatcc aagcgttggg ggtcctgagg ccagcctaag tcgcttcaaa      120
atggaacgaa ggcgtttgcg gggttccatt cagagccgat acatcagcat gagtgtgtgg      180
acaagccac ggagacttgt ggagctggca gggcagagcc tgctgaagga tgaggccctg      240
gccattgccg ccctggagtt gctgcccagg gagctcttcc cgccactctt catggcagcc      300
tttgacggga gacacagcca gacctgaag gcaatggtgc aggcctggcc cttcacctgc      360
ctccctctgg gagtgtgat gaaggacaa catctt

```

<210> 154

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 154

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acagcaaacc tctcacagc ccactggtcc tcaagagggg cnactcttc acacatcanc      60
acaactacgc attgcctccc tncactcgga aggactatcc tgctgccaag agggtaagt      120
tggaacagtgt cagagtccctg agacagatca gcaacaaccg aaaatgcacc agccccaggt      180
cctcgacac cgaggagaat gtcaagaggc gaacacacaa cgtcttgag cgccagagga      240
ggaacgagct aaaacggagc ttttttggcc tgctgacca gatcccgag ttggaaaaca      300
atgaaaaggc cccaaggta gttatcctta aaaaagccac agcatacatc ctgtccgtcc      360
aagcagagga gcaaaagctc atttctgaag aggact

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<210> 155

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 155

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tttttttttt tgaananaca ggtctttaat gtacggagtc tcacaaggca caaacacct      60
caccaggacc aaataaataa ctccacggtt gcaggaaggc gcggtctggg gaggatgcgg      120
catctgagct ctcccagggc tggtagggcg gccgggggtc tgcatctgt gaggggcctc      180
ctgggtgtgt cgggcctct anagcgggtc cagtctccag gatggggatc gctcactcac      240
tctccgagtc ggagtagtcc gccacgaggg aggagccgan actgcagggg tgccgcgtgt      300
cgggggtgtc agctgcctcc tgggaggagc ctgctggcna caggggcttg tcctgacggc      360
tcccttctg cccctcggg ctgctgcact tggggg

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<210> 156

<211> 396

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 156
 gaaggggggc ngggcagggg cggaatgtan anattantgc catgattgaa gattttaagaa 60
 acgtgagatt caggattttc accacatccc catttagtta gcttgctcgt ttggctgggtg 120
 caaatgccag atggattatg aacaatgaca gttaaattaat gcaacataat caggtaatga 180
 tgccaagcgt atctgggtgtt ccagggtattg tacctttacc ggaacaaatc agtaaatcca 240
 caatccctgg cacctgttag gcagctatta acctagtaaa tgctccccc tcccatctca 300
 atcagcaang acaatcaaaa acatttgctt tnagtggcag gaacactggt acatttttac 360
 ttgctccaag ggctgtgcca acgtccctc tctctg 396

<210> 157
 <211> 396
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(396)
 <223> n = A,T,C or G

<400> 157
 tttttttttt tttttgggga atgtaaatct tttattaaaa cagttgtctt tccacagtag 60
 taaagctttg gcacatacag tataaaaaat aatcacccac cataattata ccaaattcct 120
 nttatcaact gcatactaag tgttttcaat acaatttttt ccgtataaaa atactgggaa 180
 aaattgataa ataacaggtg ananaaagat atttctaggg aattactagg atcatttgga 240
 aaaagtgagt actgnggata tttaaaatat cacagtaaca agatcatgct tgttcctaca 300
 gtattgcggg ccanacactt aagtgaagc anaagtgttt gggtgacttt cctacttaaa 360
 attttggncat tatcatttca aaacatttgc atcttg 396

<210> 158
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 158
 tttccgaaga cgggcagctt cagagaagag gattattcgg gagattgctg gtgtggccca 60
 tagactcttt ggcatagact ctttcgcagg cagccactct gagtggtggc agttctataa 120
 ccatcccca actagctgga gcctgatgga taggaacggg tagtctgtcc tcttccccat 180
 aaaaatgttc caaaaagtta tctccagaga gagtccctta tgaagacagt tgccaagctg 240
 tattctcatt ctttaaacca ataccaggt cagggctagt tcacactagc actgttaggg 300
 acatgggtgtg gctagaaatg aattgagtgt gacttctccc tacaaccca ggcccaggga 360
 taggaggagg cagaggggtg cctggagtgt ctgcac 396

<210> 159
 <211> 396
 <212> DNA
 <213> Homo sapien

<400> 159
 tccgcgcgtt gggaggtgta gcgcggctct gaacgcgctg agggccgttg agtgtcgcag 60
 gcggcgaggg cgcgagttag gagcagaccc aggcacgcg cgccgagaag gccgggcgtc 120

```

ccacactga aggtccggaa aggcgacttc cgggggcttt ggcacctggc ggaccctccc 180
ggagcgctcg cacctgaacg cgaggcgctc cattgcgcgt gcgcgttgag gggcttcccg 240
cacctgatcg cgagacccca acggctgggtg gcgtcgcttg cgcgtctcgg ctgagctggc 300
catggcgag ctgtgcgggc tgaggcgag ccggggcttt ctgcacctgc tgggatcgct 360
gtcctctct ggggtcctgg cgcccgaccg agaacg 396

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<210> 160

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 160

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ggaaaccttc tcaactaaga gaacatcatt tctggcaaac tatttttggt agtcacaat 60
atatgtcgta cactctacaa tgtaaatagc actganccac ancttacaga aggtaaaaag 120
angnataana acttccttta caaaanantt cctgttggtt ttaatactcc ccattgctta 180
tganaattnt ctatangtct ctcangantg ttgcaccca tttctttnt aacttctact 240
aaaaanccat ttacattgna nagtgtaacna cntatatttg ngagctaaca aaaaatngtt 300
ttcnganat gatgttcttt tagtttnaga nggttcnnnc aanttnctac tccngcccg 360
cactgnncnc cacatttnnn naattacacc ncacng 396

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<210> 161

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 161

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tttttggttg attattttta ttataatgaa attaaactta tgactattac agtatgctca 60
gcttaaaaaa tttatgagta ctgcaaggac taacagaaac aggaaaaatc ctactaaaaa 120
tatttggtga tgggaaatca ttgtgaaagc aaacctcaa atattcattt gtaagccata 180
agaggataag cacaaccata tgggaggaga taaccagtct ctcccttcac atatattctt 240
ttttatttct tggtatacct tcccaaaaca nanacattca acagtagtta gaatggccat 300
ctcccaacat tttaaaaaaa ctgcnccccc caatgggtga acaaagtaaa gagtagtaac 360
ctanagttca gctgagtaag ccactgtgga gcctta 396

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<210> 162

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 162

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tttttttttt tttttttttt tttttttttt ttnggggncc aaattttttt ntttgaagga      60
angggacaaa nnaaaaaact taaggggntg ttttggnncn acttanaaaa aagggaaagg      120
aaaccccaac atgcatgccc tnccttgggg accanggaan ncnccccncn ggtntgggga      180
aantaaccn aggnttaact ttnattatca ctgncnccca gggggggcctt nnaaaaaaaaa      240
nnttccccca anccaaantn gggnnncncc attttncnca anttggnncn cnggncnccc      300
nattttttga ngggtttcnc cngcncattn aggggaanggg nntcaannaa accncncaaa      360
nggggggnnat ttttntcang ggccnatttg ngcnnt      396

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<210> 163

<211> 396

<212> DNA

<213> Homo sapien

<400> 163

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cactgtccgg ctctaacaca gctattaagt gctacctgcc tctcaggcac tctcctcgcc      60
cagtttctga ggtcagacga gtgtctgcga tgtcttccc cactctattc cccagcctc      120
tttctgcttt catgctcagc acatcatctt cctaggcagt ctcttcccca aagtctcacc      180
ttttcttcca atagaaaatt ccgcttgacc tttgggtgcac tggccacttc ccagctccac      240
tggcccaagt ctgagccgga ggcccttggt ttgggggagg ggggagagt ggatgtgatt      300
gcccttgaag aacaaggctg acctgagagg ttcttggcgc cctgaggtgg ctcagcacct      360
gccagggta ggctggcat gaggggttag gtcagc      396

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<210> 164

<211> 396

<212> DNA

<213> Homo sapien

<400> 164

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gacacgcggc ggtgtcctgt gttggccatg gccgactacc tgattagtgg gggcacgtcc      60
tacgtgccag acgacggact cacagcacag cagctcttca actgcggaga cggcctcacc      120
tacaatgact ttctcattct ccctgggtac atcgacttca ctgcagacca ggtggacctg      180
acttctgctc tgaccaagaa aatcactctt aagacccac tggtttcctc tcccatggac      240
acagtcacag aggctgggat ggccatagca atggcgctta caggcggtat tggcttcac      300
caccacaact gtacacctga attccaggcc aatgaagttc ggaaagtga gaaatatgaa      360
cagggattca tcacagacc tgtggtcctc agcccc      396

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<210> 165

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(396)

<223> n = A,T,C or G

<400> 165

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tttttttttt tttttttttt ttttttcang ggnccactgag gctttttatt ttgancncaa      60
aaccnccggg gatctancct gnggcncncc cggaaatnac ncnaggctca catnactnta      120
aacncttggg ggaaaggagg gcaaaaaaaaa caatgacttg ggccaattnc ncnactgcaa      180
agntananct gccaacaggg ctccaggagg cttggnntnt gtaaaanttn taaggaagcg      240
gnncnaactc cncggggggg gggcnctaac tancagggac ccctgcaagn gttggncggg      300
ggcctcaacc tgctgagct nacncaaggg gnggggntn tntanccaac aggggaccna      360
agggcttgcc tnccacagn ttacttggcc aagggy      396

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<210> 166
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)
<223> n = A,T,C or G

<400> 166
ttttttcaaa ttcagagcat ttttattaaa agaacaaaat attaaggcac aaaatacatc 60
aatttttcaa atgaaaaccc ttcaaacggt tatgtcctac attcaacgaa acttcttcca 120
aattacggaa taattttaact ttttaaaata naaaaatata agttcttaaa tgccataaat 180
ttctcccaa ataatgttt tcttagtttt aatgaagtct ctcatgcag tactgagctc 240
caatattata atgtncactt ccttaaaaat ctagttttgc cacttatata cattcaatat 300
gtttaaccag tatattaacc agtatattaa ccaatatgtt aaacttcttt taagtataag 360
gcttggtatt ttgtattgct tattgcatgc ttgat 396

<210> 167
<211> 396
<212> DNA
<213> Homo sapien

<400> 167
tgccggcagc ggcggtggcg gtggctgagc agaggacccg gcgggcggcc tcgcggtca 60
ggacacaatg tttgcacgag gactgaagag gaaatgtgtt ggccacgagg aagacgtgga 120
gggagccctg gccggcttga agacagtgtc ctcatacagc ctgcagcggc agtcgctcct 180
ggacatgtct ctggtgaagt tgcagctttg ccacatgctt gtggagccca atctgtgccg 240
ctcagtcctc attgccaaca cgggtccggca gatccaagag gagatgacgc aggatgggac 300
gtggcgccca gtggcaccac aggtgcaga gcgggcggcg ctcgaccgct tgggtctccac 360
ggagatcctg tgccgtgcag cgtgggggca agaggg 396

<210> 168
<211> 396
<212> DNA
<213> Homo sapien

<400> 168
taggatggta agagtattat aaggattggt acaaggcatg atgagtcctt ttgcttttag 60
gcttttgact tctggtttta gactttcttt agcttctgtt gttagacaac attgtgcaag 120
cttggttttt ataagtttgc atggattaaa ctgaacttaa tgaaattgtc cctcccccca 180
aattctcagc acaattttta ggcccacaag gagtcaagca cctcaaggag atcttcagtt 240
tgaacttggt gtagacacag ggatactgat gaatcaatat tcaaattagc tgttacctac 300
ttaagaaaga gaggagacct tggggatttc gaggaagggt tcataaggga gatttttagct 360
gagaaatacc atttgacagc tcaatcactt ctgacc 396

<210> 169
<211> 396
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(396)

<223> n = A,T,C or G

<400> 169

tttttttttt	tttcanaatt	aaattcttta	atacaaatg	cttttttttt	tttaaaanat	60
atctgtat	ctttgncgtt	gttnaaaaat	aaatatgtnc	tacggaatat	ntcnaaaaac	120
tgcnctaaaa	acaaanacgn	gatgttaata	tcttttcccc	ncaattntta	cggataaaca	180
gtancccccna	taaataaatg	atancnaatn	ttaaaattaa	aaaagganan	anatttagta	240
tgnaaaattc	tctatttttt	cttggttttg	ttttncntat	aaaaaacana	atagcaatgt	300
ntntttttatc	anaatcccnt	ntntncctaa	acnttttttt	ttttntttnc	ccccnaatnc	360
aagnngccaa	anatntntnt	agnatgnana	tgtntn			396

<210> 170

<211> 396

<212> DNA

<213> Homo sapien

<400> 170

tgagaagtac	catgccgctt	ctgcagagga	acaggcaacc	atcgaacgca	acccctacac	60
catcttccat	caagcactga	aaaactgtga	gcctatgatt	gggctggtac	ccatcctcaa	120
gggaggccgt	ttctaccagg	tccctgtacc	cctaccgcac	cggcgctcgcc	gcttccctagc	180
catgaagtgg	atgatcactg	agtgccggga	taaaaagcac	cagcggacac	tgatgccgga	240
gaagctgtca	cacaagctgc	tggaggtctt	ccataaccag	ggccccgtga	tcaagaggaa	300
gcatgacttg	cacaagatgg	cagaggccaa	ccgtgccctg	gccccactacc	gctgggtggtg	360
gagtctccag	gaggagccca	gggccctctg	cgcaag			396

<210> 171

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 171

ggtcctcgtc	gtggtgagcg	cagccactca	ggctggctct	gggggtgggg	ctgtagggga	60
aagtgtctaaa	gccgctgagt	gaagtaagaa	ctctgctaga	gaggaaaatg	ggcttgcttt	120
catcatcatc	ctnctcagct	gggtgggtca	agtgggaagt	tctgtcactg	ggatctggtt	180
cagtgtctca	agaccttgcc	ccaccacgga	aagccttttt	caentacccc	aaaggacttg	240
gagagatggt	agaagatggn	tctnaaanat	tcctctgcna	atntgttttt	agctatcaag	300
tggtctcccc	ccttaancag	gnaaaacatg	atcagcangt	tgctcggatg	gaaaaactan	360
cttggtttgn	naaaaaanct	ggaggcttga	caatgg			396

<210> 172

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 172

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agccttgggc caccctcttg gagcatctgg ctgtcgaatt cttgtgaccc tgttacacac      60
actggagaga atgggcagaa gtcgtggtgt tgcagccctg tgcattgggg gtgggatggg      120
aatagcaatg tgtgttcaga gagaatgaat tgcttaaact ttgaacaacc tcaatttctt      180
tttaaactaa taaagtacta ggttgcaata tgtgaaaaaa aaaaaaaaag ggcggcognt      240
cnantntana gggcccnttn aaacccgttg atcaacctcg actgtgcctt ctagttgcca      300
gccatctgtt gttngccctt ccccggtgnc tttcttgacc ttgaaagggg ccccnccctt      360
gtctttccta anaaaaanga agaantnncc ttccnt                                396

```

<210> 173

<211> 396

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (396)

<223> n = A,T,C or G

<400> 173

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aagcatgtgg atatgttttag ctacgtttac tcacagccag cgaactgaca ttaaaataac      60
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aatgactttt tgaaagtaaa agcagcataa agaatttgtc acaggaaggc tgtctcagat      180
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<210> 174

<211> 924

<212> DNA

<213> Homo sapiens

<400> 174

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<210> 175

<211> 3321

<212> DNA

<213> Homo sapiens

<400> 175

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<211> 487

<212> DNA

<213> Homo sapiens

<400> 176

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<210> 177

<211> 3999

<212> DNA

<213> Homo sapiens

<400> 177

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<211> 1069

<212> DNA

<213> Homo sapiens

<400> 178

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<210> 179

<211> 1817

<212> DNA

<213> Homo sapiens

<400> 179

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<210> 180

<211> 2382

<212> DNA

<213> Homo sapiens

<400> 180

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<210> 181

<211> 2377

<212> DNA

<213> Homo sapiens

<400> 181

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<211> 1370

<212> DNA

<213> Homo sapiens

<400> 182

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<212> DNA

<213> Homo sapiens

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<400> 183

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<210> 184
<211> 3079
<212> DNA
<213> Homo sapiens

<400> 184

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<210> 185

<211> 3000

<212> DNA

<213> Homo sapiens

<400> 185

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<210> 186

<211> 807

<212> PRT

<213> Homo sapiens

<400> 186

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Val	Phe	Trp	Ile	Ala	Pro	Pro	Ala	Gly	Thr	Gly	Cys	Val	Ile	Leu	Lys	145	150	155
Ala	Ser	Ile	Val	Gln	Lys	Arg	Ile	Ile	Tyr	Phe	Gln	Asp	Glu	Gly	Ser	165	170	175
Leu	Thr	Lys	Lys	Leu	Cys	Glu	Gln	Asp	Ser	Thr	Phe	Asp	Gly	Val	Thr	180	185	190
Asp	Lys	Pro	Ile	Leu	Asp	Cys	Cys	Ala	Cys	Gly	Thr	Ala	Lys	Tyr	Arg	195	200	205
Leu	Thr	Phe	Tyr	Gly	Asn	Trp	Ser	Glu	Lys	Thr	His	Pro	Lys	Asp	Tyr	210	215	220

Pro Arg Arg Ala Asn His Trp Ser Ala Ile Ile Gly Gly Ser His Ser
 225 230 235 240
 Lys Asn Tyr Val Leu Trp Glu Tyr Gly Gly Tyr Ala Ser Glu Gly Val
 245 250 255
 Lys Gln Val Ala Glu Leu Gly Ser Pro Val Lys Met Glu Glu Glu Ile
 260 265 270
 Arg Gln Gln Ser Asp Glu Val Leu Thr Val Ile Lys Ala Lys Ala Gln
 275 280 285
 Trp Pro Ala Trp Gln Pro Leu Asn Val Arg Ala Ala Pro Ser Ala Glu
 290 295 300
 Phe Ser Val Asp Arg Thr Arg His Leu Met Ser Phe Leu Thr Met Met
 305 310 315 320
 Gly Pro Ser Pro Asp Trp Asn Val Gly Leu Ser Ala Glu Asp Leu Cys
 325 330 335
 Thr Lys Glu Cys Gly Trp Val Gln Lys Val Val Gln Asp Leu Ile Pro
 340 345 350
 Trp Asp Ala Gly Thr Asp Ser Gly Val Thr Tyr Glu Ser Pro Asn Lys
 355 360 365
 Pro Thr Ile Pro Gln Glu Lys Ile Arg Pro Leu Thr Ser Leu Asp His
 370 375 380
 Pro Gln Ser Pro Phe Tyr Asp Pro Glu Gly Gly Ser Ile Thr Gln Val
 385 390 395 400
 Ala Arg Val Val Ile Glu Arg Ile Ala Arg Lys Gly Glu Gln Cys Asn
 405 410 415
 Ile Val Pro Asp Asn Val Asp Asp Ile Val Ala Asp Leu Ala Pro Glu
 420 425 430
 Glu Lys Asp Glu Asp Asp Thr Pro Glu Thr Cys Ile Tyr Ser Asn Trp
 435 440 445
 Ser Pro Trp Ser Ala Cys Ser Ser Ser Thr Cys Asp Lys Gly Lys Arg
 450 455 460
 Met Arg Gln Arg Met Leu Lys Ala Gln Leu Asp Leu Ser Val Pro Cys
 465 470 475 480
 Pro Asp Thr Gln Asp Phe Gln Pro Cys Met Gly Pro Gly Cys Ser Asp
 485 490 495
 Glu Asp Gly Ser Thr Cys Thr Met Ser Glu Trp Ile Thr Trp Ser Pro
 500 505 510
 Cys Ser Ile Ser Cys Gly Met Gly Met Arg Ser Arg Glu Arg Tyr Val

515	520	525
Lys Gln Phe Pro Glu Asp Gly Ser Val Cys Thr Leu Pro Thr Glu Glu 530 535 540		
Met Glu Lys Cys Thr Val Asn Glu Glu Cys Ser Pro Ser Ser Cys Leu 545 550 555 560		
Met Thr Glu Trp Gly Glu Trp Asp Glu Cys Ser Ala Thr Cys Gly Met 565 570 575		
Gly Met Lys Lys Arg His Arg Met Ile Lys Met Asn Pro Ala Asp Gly 580 585 590		
Ser Met Cys Lys Ala Glu Thr Ser Gln Ala Glu Lys Cys Met Met Pro 595 600 605		
Glu Cys His Thr Ile Pro Cys Leu Leu Ser Pro Trp Ser Glu Trp Ser 610 615 620		
Asp Cys Ser Val Thr Cys Gly Lys Gly Met Arg Thr Arg Gln Arg Met 625 630 635 640		
Leu Lys Ser Leu Ala Glu Leu Gly Asp Cys Asn Glu Asp Leu Glu Gln 645 650 655		
Val Glu Lys Cys Met Leu Pro Glu Cys Pro Ile Asp Cys Glu Leu Thr 660 665 670		
Glu Trp Ser Gln Trp Ser Glu Cys Asn Lys Ser Cys Gly Lys Gly His 675 680 685		
Val Ile Arg Thr Arg Met Ile Gln Met Glu Pro Gln Phe Gly Gly Ala 690 695 700		
Pro Cys Pro Glu Thr Val Gln Arg Lys Lys Cys Arg Ile Arg Lys Cys 705 710 715 720		
Leu Arg Asn Pro Ser Ile Gln Lys Pro Arg Trp Arg Glu Ala Arg Glu 725 730 735		
Ser Arg Arg Ser Glu Gln Leu Lys Glu Glu Ser Glu Gly Glu Gln Phe 740 745 750		
Pro Gly Cys Arg Met Arg Pro Trp Thr Ala Trp Ser Glu Cys Thr Lys 755 760 765		
Leu Cys Gly Gly Gly Ile Gln Glu Arg Tyr Met Thr Val Lys Lys Arg 770 775 780		
Phe Lys Ser Ser Gln Phe Thr Ser Cys Lys Asp Lys Lys Glu Ile Arg 785 790 795 800		
Ala Cys Asn Val His Pro Cys 805		

<210> 187
<211> 892
<212> DNA
<213> Homo sapiens

<400> 187
tttattgatg tttcaacagg cacttattca aataagttat atatttgaaa acagccatgg 60
taagcatcct tggcttctca cccattcctc atgtggcatg ctttctagac tttaaaatga 120
ggtagcctga atagcactaa gtgctctgta agctcaagga atctgtgcag tgctacaaag 180
cccacaggca gagaaagaac tcctcaagtg cttgtggtca gagactaggt tccatattgag 240
gcacacctat gatgaaggtc ttcacctcca gaaggtgaca ctgttcagag atcctcattt 300
cctggagagt gggagaaaat cctccttttg ggaaatccct tttcccagca gcagagccca 360
cctcattgct tagtgatcat ttggaaggca ctgagagcct tcaggggctg acagcagaga 420
aatgaaaatg agtacagttc agatggtgga agaagcatgg cagtgcacac ttccatgctc 480
tttttctcag tgtctgcaac tccaaagatc aaggccataa cccaggagac catcaacgga 540
agattagttc tttgtcaagt gaatgaaac caaaagcacg catgagacca atgaaagttt 600
ccgcctgttg taaaatctat tttccccaag ggaaagtcct tgcacagaca ccagtgcagtg 660
agttctaaaa gatacccttg gaattatcag atcagaaac ttttattttt tttttctgta 720
acagtctcac gagacttctc ataattgctc taatatattg cacttttcta atcaaagtgc 780
gagtttatga gggtaaaagt ctactttcct actgcagcct tcagattctc atcattttgc 840
atctattttg tagccaataa aactccgcac tagcaaaaaa aaaaaaaaaa aa 892

<210> 188
<211> 1448
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1) ... (1448)
<223> n = A,T,C or G

<400> 188
tgtgactcac atttctttta ctgtgacaca ataattgtgat cctaaaactg gcttatcctt 60
gagtgtttac aactcaaaca actttttgaa tgcagtagtt tttttttttt aaaaacaaac 120
ttttatgtca aatttttttt cttagaagta gtcttcatta ttataaattt gtacaccaa 180
aggccatggg gaactttgtg caagtacctc atcgctgagc aaatggagct tgctatgttt 240
taatttcaga aaatttcctc atatacgtag tgtgtagaat caagtctttt aataattcat 300
tttttcttca taatatttac tcaaagttaa gcttaaaaaa aagttttatc ttaaaatcat 360
atttgaagac agtaagacag taaactattt taggaagtca acccccattg cactctgtgg 420
cagttattct ggtaaaaata ggcaaaagtg acctgaatct acaatgggtg cccaaagtaa 480
ccaagtaaga gagattgtaa atgataaacc gagcttttaa ggataaagtg ttaataaaga 540
aagggaagctg ggcacatgtc aaaaaggagg atcgaaatgt taggtaatca tttagaaagg 600
acagaaaata tttaaagtgg ctcataggta atgaatatct ctgacttaga tgtaaatcca 660
tctggaatct ttacatcctt tgccagctga aacaagaaaag tgaagggaca atgatatttc 720
atggctcagtt tattttgtaa gagacagaag aaattatatc tatacattac cttgtagcag 780
cagtacctgg aagccccagc ccgtcacaga agtgtggagg ggggctcctg actagacaat 840
ttccctagcc cttgtgattt gaagcatgaa agttctggca ggttatgagc agcactaggg 900
ataaagtatg gttttatttt ggtgtaattt aggtttttca acaaagccct tgtctaaaat 960
aaaagtcatt attggaataa tttgaaaact agaaaatgat ggataaaagg gctgataaga 1020
aaattttcga ctgtcagtag aagtgcagata agatcctcag aggaacacagt aagaagggat 1080
aatcattaag atagtaaaac aggcacagca gaatcacatg tgcncacaca catacacatg 1140
taaacattgg aatgcataag ttttaatat ttagcgctat cagtttctaa atgcattaat 1200
tactaactgc cctctcccaa gattcattta gttcaaacag tatccgtaaa ctaggataa 1260

```
tgccacatgc attcaatggg atcttttaag tactcttcag tttgttccaa gaaatgtgcc 1320
tactgaaatc aaattaatct gtattcaatg tgtacttcaa gactgctaata tgtttcatct 1380
gaaagcctac aatgaatcat tgttcamcct tgaaaaataa aattttgtaa atcaaaaaaa 1440
aaaaaaaaa 1448
```

<210> 189

<211> 460

<212> DNA

<213> Homo sapiens

<400> 189

```
ttttgggagc acggactgtc agttctctgg gaagtgggtca gcgcacccctg cagggcttct 60
cctcctctgt cttttggaga accagggctc ttctcagggg ctctagggac tgccaggctg 120
tttcagccag gaaggccaaa atcaagagtg agatgtagaa agttgtaaaa tagaaaaagt 180
ggagttgggtg aatcggttgt tctttcctca catttggtatg attgtcataa ggtttttagc 240
atgttcctcc ttttcttcac cctccccctt tttcttctat taatcaagag aaacttcaaa 300
gttaatggga tggtcggatc tcacaggctg agaactcgtt cacctccaag catttcatga 360
aaaagctgct tcttattaat catacaaaact ctcaccatga tgtgaagagt ttcacaaatc 420
cttcaaaata aaaagtaatg acttaaaaaa aaaaaaaaaa 460
```

<210> 190

<211> 481

<212> DNA

<213> Homo sapiens

<400> 190

```
aggtgggtgga agaaactgtg gcacgaggtg actgaggtat ctgtgggagc taatcctgtc 60
caggtggaag taggagaatt tgatgatggt gcagaggaaa ccgaagagga ggtggtggcg 120
gaaaatccct gccagaacca ccaactgcaa cagggcaagg tgtgcgagct ggatgagaac 180
aacaccccca tgtgctgtgt ccaggacccc accagctgcc cagcccccat tggcgagttt 240
gagaaggtgt gcagcaatga caacaagacc ttcgactctt cctgccactt ctttgccaca 300
aagtgcaccc tggagggcac caagaagggc cacaagctcc acctggacta catcgggcct 360
tgcaaataca tcccccttg cctggactct gagctgaccg aattccccct gcgcattgcg 420
gactggctca agaacgtcct ggtcaccctg tatgagaggg atgaggacaa caaccttctg 480
a 481
```

<210> 191

<211> 489

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(489)

<223> n = A,T,C or G

<400> 191

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atataaatta gactaagtgt tttcaaataa atctaaatct tcagcatgat gtgttgtgta 60
taattggagt agatattaat taagtccctt gtataatggt ttgtaatttt gcaaaacata 120
tcttgagttg tttaaacagt caaaatgttt gatattttat accagcttat gagctcaaag 180
tactacagca aagcctagcc tgcataatc taccctaaa caaagtaata gcgcctcttt 240
tattattttg actgaatggt ttatggaatt gaaagaaaca tacgttcttt tcaagacttc 300
ctcatgaatc tntcaattat aggaaaagtt attgtgataa aataggaaca gctgaaagat 360
tgattaatga actattgtta attcttctta ttttaatgaa tgacattgaa ctgaattttt 420
tgtctgttaa atgaacttga tagctaataa aaagncaact agccatcaaa aaaaaaaaaa 480
```

aaaaaaaa

489

<210> 192

<211> 516

<212> DNA

<213> Homo sapiens

<400> 192

```
acttcaaagc cagctgaagg aaagaggaag tgctagagag agcccccttc agtgtgcttc 60
tgacttttac ggacttggct tgtagaagg ctgaaagatg atggcaggaa tgaaaatcca 120
gcttgatgc atgctactcc tggctttcag ctctggagt ctgtgctcag attcagaaga 180
ggaaatgaaa gcattagaag cagatttctt gaccaatatg catacatcaa agattagtaa 240
agcacatgtt cctcttgga agatgactct gctaaatgtt tgcagtcttg taaataattt 300
gaacagccca gctgaggaaa caggagaagt tcatgaagag gagcttggtg caagaaggaa 360
cttcttactg ctttagatgg ctttagcttg gaagcaatgt tgacaatata ccagctccac 420
aaaatctgtc acagcagggc ttttcaacac tgggagttaa tccaggaaga tattcttgat 480
actggaaatg acaaaaatgg aaaggaagaa gtcata 516
```

<210> 193

<211> 1409

<212> DNA

<213> Homo sapiens

<400> 193

```
tgattctttt ccaaaacttt tagccatagg gtcttttata gacagggata gtaaaatgaa 60
aattgagaaa tataagatga aaaggaatgg taaaaatata ttttaggggg cttttaattg 120
gtgatctgaa atcttgggag aagctgttct tttcaggcct gaggtgctct tgactgtcgc 180
ctgcgcactg tgtacccgga gcaacattct aagggtgtgc tttcgccttg gctaactcct 240
ttgacctcat tcttcatata gtagtctagg aaaaagtgc aggtaattha aactgtctag 300
tggtacatag taactgaatt tctattccta tgagaaatga gaattattta tttgccatca 360
acacatttta tactttgcat ctccaaattt attgcggcga gacttgcca ttgtgaaagt 420
tagagaacat tatgtttgta tcatttcttt cataaaacct caagagcatt ttaagccct 480
tttcatcaga ccagtgaaa actaaggata gatgtttttt aactggaggt ctctgataa 540
ggagaacaca atccaccatt gtcatttaag taataagaca ggaaattgac cttgacgctt 600
tcttggttaa tagatttaac aggaacatct gcacatcttt tttccttggt cactatttgt 660
ttaattgcag tggattaata cagcaagagt gccacattat aactaggcaa ttatccattc 720
ttcaagactt agttattgtc aactaattg atcgtttaag gcataagatg gtctagcatt 780
aggaacatgt gaagctaata tgctcaaaaa gatcaacaaa ttaatttgt tgctgatatt 840
tgcataattg gctgcaatta tttaatgttt aattgggttg atcaaatgag attcagcaat 900
tcacaagtgc attaatataa acagaactgg ggcaacttaa atgataatga ttaacttata 960
ttgcatgttc tcttcctttc acttttttca gtgtctacat ttcagaccga gtttgtcagc 1020
ttttttgaaa acacatcagt agaaaccaag attttaaaat gaagtgtcaa gacgaaggca 1080
aaacctgagc agttcctaaa aagatttgct gttagaaatt ttctttgtgg cagtcattta 1140
ttaaggattc aactcgtgat acacaaaaag aagagttgac ttcagagatg tgttccatgc 1200
tctctagcac aggaatgaat aaatttataa cacctgcttt agcctttgtt ttcaaaagca 1260
caaaggaaaa gtgaaaggga aagagaaaca agtgactgag aagtcttggt aaggaatcag 1320
gttttttcta cctggtaaac attctctatt cttttctcaa aagattgttg taagaaaaaa 1380
tgtaagmcaa aaaaaaaaaa aaaaaaaaaa 1409
```

<210> 194

<211> 441

<212> DNA

<213> Homo sapiens

<400> 194

```
cagatttcgg tagccatctc cctccaaata tgtctctttc tgctttctta gtgcccatta 60
tttcccttcc tcctttcttc tgcactgcc atctccttct tggctttccc attgttcttt 120
aactggcctg aatgtggaat tgatatttac attttgatac gggttttttc ttggcctgtg 180
tacgggattg cctcatttcc tgctctgaat tttaaaatta gatattaaag ctgtcatatg 240
gtttcctcac aaaagtcaac aaagtccaaa caaaaatagt ttgccgtttt actttcatcc 300
attgaaaaag gaaattgtgc ctcttgagc ctaggcaaag gacatttagt actatcgatt 360
ctttccaccc tcacgatgac ttgcggttct ctctgtagaa aagggatggc ctaagaaata 420
caactaaaaa aaaaaaaaaa a 441
```

<210> 195

<211> 707

<212> DNA

<213> Homo sapiens

<400> 195

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cagaaaaata tttggaaaaa atataccact tcatagctaa gtcttacaga gaagaggatt 60
tgctaataaa acttaagttt tgaaaattaa gatgcaggta gagcttctga actaatgcc 120
acagctccaa ggaagacatg tcctatttag ttattcaaat acaagttgag ggcatgtgta 180
ttaagcaaac aatatatttg ttagaacttt gtttttaaat tactgttcc tgcattact 240
tataaagagt ctctaacttt cgatttctaa aactatgtaa tacaaaagta tagtttccc 300
atgtgataaa aggccaatga tactgagtag gatatatgcg tatcatgcta cttcattcag 360
tgtgtctgtt ttttaacta ataaggcagt ttgacagaaa ttatttcttt gggactaagg 420
tgattatcat ttttttccc ttcaaaattg tgctttaagt gctgataacc acaggcagat 480
tgcaaaagac tgataaggca acaaaagtag agaattttag gatcaaaggc atgtaactga 540
aaggtaacaa cagtacataa ggcacaactg gggaaggcag cagtgaaaca tgtttgtggg 600
gttaagttag tcattgtaaa taagggaatt gcacatttat tttctgtcga cgcggccgcc 660
actgtgtgag atatctgcag aattccacca cactggacta gtggatc 707
```

<210> 196

<211> 552

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(552)

<223> n = A,T,C or G

<400> 196

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tggccagcca gcctgatgtg gatggcttcc ttgggggtgg gcttccctca agcccgaatt 60
ngtggacatc atcaatgcca aacaatgagc cccatccatt ttccctaccc ttcctgccaa 120
gccagggant aagcagccca gaagcccagt aactgccctt tccctgcata tgcttttgat 180
ggtgtcatnt gctccttcc tgggctcat ccaaactgta tnttcttta ctgtttatat 240
nttcacctg taatggttgg gaccaggcca atccctntc cacttactat aatggttggg 300
actaaacgtc accaaggtgg cttntccttg gctgaganat ggaaggcgtg gtgggatttg 360
ctnctgggtt ccctaggccc tagtgagggc agaagagaaa ccatcctntc ccttnttaca 420
ccgtgaggcc aagatccctt cagaaggcag gagtgctgcc ctntcccatg gtgcccggtg 480
ctntgtgctg tgtatgtgaa ccacccatgt gagggaataa acctggcact aggaaaaaaa 540
aaaaaaaaaa aa 552
```

<210> 197

<211> 449

<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(449)
<223> n = A,T,C or G

<400> 197
ctccagagac aacttcgcgg tgtggtgaac tctctgagga aaaacacgtg cgtggnanca 60
agtgactgag acctanaaat ccaagcggtg gaggtcctga ggccagccta agtcgcttca 120
aaatggaacg aaggcgtttg cggggttcca ttcagagccg atacatcagc atgagtgtgt 180
ggacaagccc acggagactt gtggagctgg cagggcagag cctgctgaag gatgaggccc 240
tggccattgc ccgccctgga gttgctgccc agggagctct tcccgcact cttcatggca 300
gcctttgacg ggagacacag ccagaccctg aaggcaatgg tgcaggcctg gcccttcacc 360
tgccctccctc tgggagtgct gatgaaggga caacatcttc acctggagac cttcaaagct 420
gtgcttgatg gacttgatgt gtccttgc 449

<210> 198
<211> 606
<212> DNA
<213> Homo sapiens

<400> 198
tgagtttgcc cccttaccct catcccagtg aatatttgca attcctaaag acgtgttttg 60
attgtcacac ctgggtgggg aacatgctac tggcatctaa tgcatagagg gcagtaatgc 120
tgctaaacat ctttcaacgc acaggacaga gccccacaaa agagaattat ctagcccca 180
atgtccataa cactgctgtt gagaaaacct accgcaggat cttactgggc ttcataaggta 240
agcttgccctt tgttctggct tctgtagata tataaaataa agacactgcc cagtccctcc 300
ctcaacgtcc cgagccaggg ctcaaggcaa ttccaataac agtagaatga aactaaata 360
ttgatttcaa aatctcagca actagaagaa tgaccaacca tctggttg cctgggactg 420
tctagtttt agcattgaaa gtttcagggt ccaggaaagc cctcaggcct gggtgctgg 480
tcaccctagc agctgaggga ctcttcaata cagaattagt ctttgtgcac tggagatgaa 540
tatactttta tttgtaacat gtgaaaacat ctataaacat ctactgaagc ctgttcttgc 600
ctgcac 606

<210> 199
<211> 369
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(369)
<223> n = A,T,C or G

<400> 199
ggcaactttt tgcggattgt tcttgcttnc aggctttgcg ctgcaaatcc agtgctacca 60
gtgtgaagaa ttccagctga acaacgactg ctccctcccc gagttcattg tgaattgcac 120
ggtgaacgtt caagacatgt gtcagaaaga agtgatggag caaagtgccg ggatcatgta 180
ccgcaagtc tgtgcatcat cagcggcctg tctcatcgcc tctgcccggg accagtcctt 240
ctgctcccca gggaaactga actcagtttg catcagctgc tgcaacacct ctctttgtaa 300
cgggccaaag cccaagaaaa ggggaagtgc tgcctcggcc ctangccat ggctccgcac 360
caccatcct 369